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Treponema pallidum, an odontological point of view

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Abstract
Introduction: Syphilis is a systemic infection of sexual, blood transfusion or transplacental transmission caused by the spirochete *Treponema pallidum*.
Objective: To analyze the literature on the epidemiology, diagnostic methods, clinical and oral manifestations and treatment of *Treponema pallidum*.
Methodology: A literature review was carried out in the PubMed database with the words "*Treponema pallidum*", together with "epidemiology", "diagnosis", "clinical manifestations", "oral manifestations" and "treatment".
Results: It is estimated that each year there are 12 million new cases of syphilis worldwide and more than 90% are from developing countries. Direct detection and serological tests are the available options for identification. Infectious ulceration is the sign of primary disease, while secondary disease is characterized by multisystem involvement. Late syphilis involves neurosyphilis, cardiovascular syphilis and gummatous syphilis, which may coexist. The oral manifestation presents as one or more ulcers depending on the stage. The main treatment for syphilis is penicillin, although its effectiveness will depend on the stage of the disease.
Conclusions: Due to its increasing incidence, it is of great relevance that the dentist is familiar with the clinical appearance, especially oral, of this pathology for early diagnosis and treatment.

Keywords: syphilis, *Treponema pallidum*, oral, manifestations, diagnosis, treatment, epitheliologic, epithemiology

1. Introduction
With infectivity as high as 10-30% through sexual contact or 60% through intercourse, syphilis rates have increased 300% since 2000 in many Western countries [1]. Syphilis is a systemic infection caused by the spirochete *Treponema pallidum*, subspecies pallidum (*T. pallidum*) [2]. Due to its clinical manifestations, this disease has been named "the great imitator". Its origin is controversial and there are several theories about it [3, 4]. The epidemic spread of syphilis began in the late 15th to early 16th century due to the migration of people in Europe [4]. and was not cured until Dr. Paul Ehrlich developed his "magic bullet", arsphenamine, in 1910 [5, 6].
Syphilis is transmitted through sexual contact with infectious lesions of the mucous membranes or injured skin, by blood transfusion or via the transplacental route from a pregnant woman to her fetus [7]. This disease has three clinical stages. The primary stage is characterized by a single chancre that manifests approximately 90 days after exposure and remits spontaneously between two and eight weeks. The secondary stage occurs 2 to 12 weeks after exposure, when a rash develops on various parts of the skin. The tertiary stage is characterized by gummata and/or neurosyphilis arising three years or more after exposure [8]. The incubation period is usually 21 to 30 days after contact, although it can vary from 10 to 90 days, depending on the number and virulence of the treponemes and the host response [9].
There has been a recent resurgence in the development of oral syphilis, with oral manifestations dependent on the stage of presentation (primary, secondary and tertiary). Oral sex has contributed to the overall increase in the spread of the disease, with the highest incidence in men aged 25-29 years (88% of documented oral cases in men).

The lips, tongue, and palate are most commonly infected [10, 11].

The literature mentions that, despite the availability of diagnostic tests and the efficacy of penicillin in the treatment of this disease, syphilis is re-emerging as a global public health problem in high, middle and low-income countries. Since dentists are often the first to identify signs of systemic disease through oral manifestations, it is of great importance that they have the necessary knowledge to distinguish and detect early the presence of this pathology. Therefore, the aim of this article is to analyze the literature on the epidemiology, diagnostic methods, clinical and oral manifestations and treatment of *Treponema pallidum*.

2. Materials and Methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews (AMSTAR-2). The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words *Treponema pallidum* in conjunction with epidemiology, diagnosis, clinical manifestations, oral manifestations, and treatment. The keywords were used individually, as well as each of them related to each other.

3. Results & Discussion

3.1 Epidemiology

Syphilis was first recognized in the late 15th century, however, in the last 20 years, the incidence of this sexually transmitted disease has increased substantially [12]. There is a wide debate on the origin of this pathology. There are two hypotheses: Colombian and pre-Colombian. The first is that this disease was brought from America to Europe by Christopher Columbus' crew, while the second proposes that this pathology existed in Europe since the Hippocratic era, but was often misdiagnosed and unrecognized [13].

Although syphilis infection is easily identifiable and treatable, it continues to cause morbidity and mortality worldwide. Syphilis infection rates continue to increase among select populations in high-income countries and remain at endemic levels in low- and middle-income countries [14].

Despite the availability of effective antibiotic treatment since the mid-20th century, this bacterial infection has resurfaced globally in recent decades with an estimated 10.6 million cases in 2008 [15]. There are an estimated 12 million new cases of syphilis worldwide each year and more than 90% are from developing countries [16].

The increase in the number of primary and secondary syphilis cases in the United States has been linked to the increase in infected male patients by a factor of more than 3. In 2018, men accounted for 86% of the total number of cases with this pathology. More than half of these patients reported having had sexual intercourse with another person of the same sex. Likewise, 42% of all men were infected with the human immunodeficiency virus (HIV), a finding that highlights the association between syphilis and an increased risk of contracting HIV [17].

Similarly, cases of primary and secondary syphilis among women doubled between 2014 and 2018. In those women who used injection drugs, (e.g. methamphetamine, heroin, etc.) the number of cases increased 6 times [17]. Likewise, increasing rates have been observed among women in several countries, raising concerns about mother-to-child transmission of syphilis and congenital syphilis [18]. The increase in the rate of this disease among women of childbearing age is reflected in the increased incidence of congenital syphilis cases and infant mortality [17].

Syphilis is primarily a sexually transmitted disease that, despite the existence of an antibiotic to treat it, cases have been increasing reaching an estimated 12 million new cases of syphilis each year, mainly in male patients who have sex with another person of the same sex. There is also an increase in the incidence of congenital syphilis and it is estimated that the most affected countries are developing countries.

3.2 Diagnostic methods

Because *T. pallidum* cannot be cultured in vitro, diagnosis of syphilis based on laboratory testing generally relies on visualization of the spirochete [19].

It is due to the above that conventional diagnostic methods of this bacterium consist of direct pathogen detection and serological testing [20].

The former includes dark-field microscopy (DFM), silver staining, direct fluorescence immunoassay (DFA) and rabbit infectivity test [20]. Considered the gold standard, direct detection is the definitive diagnosis of this pathology and is very useful in suspicious lesions in serologically non-reactive patients [21]. The second type of studies includes nontreponemal and treponemal tests (e.g. TP-PA), which are used for preliminary screening and confirmation of diagnosis, respectively [20].

Currently, the Center for Disease Control and Prevention (CDC) recommend performing a TP-PA if there are discordant results between immunoassay and RPR (e.g., reactive to EIA, nonreactive to RPR) [22]. However, regardless of which diagnostic test is used, it is important to consider the sensitivity and specificity of these tests in clinically characterized sera stratified by syphilis stage for laboratories to select the most appropriate treponemal tests [23]. Likewise, it is important to remember that treponemal tests do not distinguish active treated infections, so they generally remain positive for life [1].

Both early diagnosis and early treatment are important to prevent progression from early to later stages, thereby reducing disease morbidity and mortality [24]. However, it is necessary to remember that the incubation period has a length of between 10 and 90 days. During this time, serological results may be negative [25].

The diagnosis of syphilis is based on the confirmation of the clinical impression by laboratory studies. Likewise, due to its similarity with other lesions, in dentistry it can be confused with other pathologies, so its clinical suspicion is confirmed with objective tests. Direct detection and serological tests are the options available for its identification, however, the former is the study of preference especially if the patient is in his incubation period, in which serological tests could be negative.

3.3 Clinical manifestations

Syphilis is classified as acquired and congenital. The former is further divided into early (primary and secondary), early latent (<2 years of infection) and late (>2 years of infection). The second is divided into early (diagnosed the first two years of life) and late, or less common tertiary, (present after age 2 years) [26, 27]. It is important to remember that the spirochete has a long latency period during which individuals have no signs or symptoms, but may remain infectious [28].

The clinical presentations of syphilis, in all phases, are varied, and most scholars in this area consider it "the great imitator" [29]. This is because the manifestations histologically and clinically mimic a wide variety of infectious, neoplastic and immune diseases. As a result, the diagnosis of this pathology becomes a challenge for the professional, delaying the diagnosis or missing it [30].

The infectious ulcer (chancre), the sign of the primary disease, develops after an incubation of usually 3 weeks (range 10 to 90 days) and resolves 3 to 8 weeks later [31]. Classically, the chancre is found in the anogenital region, is single, painless and indurated with a clean base that discharges a clear serum. However, chancres can be multiple, painful, purulent, destructive, extra-genital (most often oral) and can cause Follman's syphilitic balanitis [26]. Without treatment, 25% of patients develop signs of secondary syphilis [31].

Secondary syphilis is characterized by multi-systemic involvement during the first two years of infection, with manifestations first appearing about eight weeks after transmission. The rash of secondary syphilis is initially roseolar or macular, with more long-lasting lesions becoming papular or nodular [26]. Likewise, it presents symptoms such as headache, lacrimation, nasal discharge, pharyngitis, generalized arthralgia and myalgia [32]. Secondary syphilis resolves spontaneously in 3-12 weeks and the disease enters an asymptomatic latent stage [31].

Approximately one-third of untreated patients will subsequently develop symptomatic late syphilis. Incubation periods vary between 5 and 30 years after secondary syphilis and are classified into neurosyphilis, cardiovascular syphilis, and gummatous syphilis, but which may coexist. Tertiary syphilis is a term often used synonymously with late symptomatic syphilis, but generally excludes meningovascular syphilis [24,26].

Syphilis can be confused with others due to its clinical and histologic appearance. Untreated pathology evolves through three clinical stages of infection: primary, secondary, and tertiary. Each of these has different incubation times in which the patient may be unaware that he/she is infected and thus, transmit it to others.

3.4 Oral manifestations

Although primary syphilis commonly involves the genitalia, oral manifestations are seen in 4-12% of patients [33]. The early primary presentation is of a painless and usually solitary ulcer (chancre) that forms approximately 3 weeks after inoculation and typically lasts 3-7 weeks [11,33]. The ulcer may present with a yellow transudate, with infiltration of the base and hardened high margins. Erythema, edema, and petechial hemorrhage may also be present and is associated with painless regional lymphadenopathy. The vermilion and mucosa of the lips and the dorsum and lateral border of the tongue are the most frequent locations [34]. It is important to remember that different latency periods may occur between stages with the risk of causing the treating physician to have the erroneous illusion of successful treatment in case of misdiagnosis [35].

A patient's oral mucosa can be affected in all three stages, but is most common in the secondary stage [36]. This is estimated to occur in approximately 25% of untreated patients, usually several weeks to a few months after the primary stage [37] and is the stage at which oral syphilis is most commonly diagnosed [11]. Likewise, since the secondary stage is due to systemic spread of spirochetes beyond the site of primary infection, early treatment during the primary stage is important [35].

In the second stage, the two most common oral lesions are enanthema and mucosal plaques, the latter being the most frequent. Mucosal plaques are oval or serpiginous, slightly raised erosions with presence of fissures or superficial ulcers with erythematous border. There are overlapping silvery-gray or white membranous exudates [34]. Secondary oral syphilitic lesions are usually multiple and more diversified than the single ulcer of the primary stage. However, a single lesion may be the only manifestation appearing in the secondary stage [36]. Secondary stage oral lesions are typically painful and may be accompanied by skin eruptions, and the duration varies from 4 to 10 weeks [34]. Likewise, the most affected sites are the tongue, lips and commissure [32]. Similarly, in the absence of other secondary features of syphilis (exanthema, lymphadenopathy and condyloma lata), oral findings may serve as the only clinical clue to this pathology [38].

Tertiary syphilis can develop at any time up to 15 years after the initial infection, showing gummas (granulomatous inflammation) of the palate and/or tongue with atrophic luetic glossitis [11]. There may be eventual bone destruction, palatal perforation and oro-nasal fistulas [34].

Due to its clinical similarity with other pathologies, it is necessary that a differential diagnosis be made with: an atypical aphthous ulcer, fungal infection, granuloma, pemphigus, pemphigoid, traumatic ulcer, ulcerative or bulous lichen planus, squamous cell carcinoma [27].

Oral manifestations of syphilis can present in the oral cavity at any stage, the second being the most frequent. It is important to perform a differential diagnosis because ulcers can be confused with other pathologies, which would delay the diagnosis and correct treatment of these lesions. It is also important to remember that, sometimes, the oral manifestation of this pathology can be the only sign that the patient is infected, being the dentist responsible for its correct identification and management.

3.5 Treatment

Syphilis control depends primarily on the timely diagnosis and treatment of infected individuals [22]. Without a treatment that matches its efficacy, the antibiotic of choice for early syphilis is penicillin (BPG) [39].

For early syphilis (primary, secondary or early latent), a single injection of 2.4 million units of benzathine benzylpenicillin is recommended. In those patients with late latent syphilis or syphilis of unknown duration, it is recommended to administer 2.4 million units of this drug per week for 3 consecutive weeks. Higher doses of treatment are recommended in patients with neurosyphilis, in whom the literature recommends 18-20 million units per day divided into several doses every 4 hours for 10 to 14 days. Likewise, some professionals recommend that, in these patients, once this treatment has been completed, 2 to 3 doses of benzathine benzylpenicillin should also be applied as in late infections. In the case of non-pregnant patients with allergy to beta-lactam antibiotics, doxycycline or tetracycline is recommended for 14 to 28 days, depending on the stage of infection [40].

For pregnant patients, it is recommended to add a second injection of penicillin G benzathine one week after the initial dose for early stage disease due to its altered pharmacokinetics that prevents prolonged action of this drug [41]. In these patients, the efficacy of treatment depends on the stage of syphilis and the gestational age at the time of treatment. There is 100% efficacy in the primary, late latent

and tertiary stage; 95% in the secondary latent and tertiary stage; and 100% in those treatments initiated before 18 to 20 weeks of infection [42].

On the other hand, although penicillin (BPG) proved to be effective in the early manifestations of the disease and, consequently, its contagiousness, doubts remain about its ability to prevent late complications and provide microbiological eradication in vivo [43]. Likewise, it is important to remember that all patients should be offered screening for other sexually transmitted diseases, including HIV [44].

On the other hand, it is necessary to follow up the response to treatment by means of a quantitative VDRL test at 6 and 12 months in the case of primary syphilis, at 6, 12 and 24 months in latent syphilis and if the patient is infected with HIV, it should be performed every 3, 6, 9, 12 and 24 months [45]. Likewise, because there is no vaccine to prevent this disease, it is important to include sex education and promotion of condom use to prevent infection in syphilis control programs [19].

The main treatment for syphilis is penicillin. Long-acting benzathine benzylpenicillin is preferred in most cases, however, it is important to remember that its effectiveness will depend on the stage of the disease. It is also necessary to monitor the response to this treatment and perform VDRL tests to see if it is being effective against the bacteria.

4. Conclusions

Syphilis is primarily a sexually transmitted disease that, despite the existence of an antibiotic to treat it, cases have been increasing in recent years. Direct detection and serological tests are the options available for its identification. Untreated pathology evolves through three clinical stages of infection: primary, secondary and tertiary, and oral manifestations can occur in the oral cavity at any stage, the second being the most frequent. It is also important to make a differential diagnosis because ulcers can be confused with other pathologies. The main treatment for syphilis is penicillin, although it is important to remember that its effectiveness will depend on the stage of the disease. It is of great importance that the dentist is familiar with the clinical appearance, especially oral, of this pathology for early diagnosis and treatment.

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