LITERATURE REVIEW

ORAL MANIFESTATIONS OF SYPHILIS: ESSENTIAL ASPECTS FOR THE DENTIST

MANIFESTAÇÕES ORAIS DA SÍFILIS: ASPECTOS ESSENCIAIS PARA O CIRURGIÃO-DENTISTA

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ABSTRACT

Syphilis, or lues, is a chronic infectious disease caused by the spirochete *Treponema pallidum* and transmitted through sexual, via blood or placental contact. Untreated syphilis spreads to many organs and compromises the cardiovascular and nervous systems, which can result in death. The aim of this study was to describe the main aspects of syphilis for the dentist, in order to facilitate its early identification and management. To this end, literature searches were carried out on the Pubmed, Embase, Lilacs and Cochrane databases. In total, 6,265 references were found and, after reading the titles and abstracts, 40 articles were selected for full-text reading. Syphilis traditionally progresses in three stages. Primary syphilis is marked by chancre, most commonly affecting the lip. Oral manifestations are more frequent in secondary syphilis, and consist of white mucous patches, condyloma lata, maculopapular lesions or split papules. In tertiary syphilis, gummas may be present, which can cause perforations in the palate or lesions in the tongue, such as interstitial glossitis and luetic glossitis. Congenital syphilis, in turn, significantly affects children's dentition. The dentist plays an essential role in the early identification of syphilis and the consequent referral o specialized care.

Keywords: Syphilis; Treponema pallidum; Hutchinson teeth; Pathology, Oral; Sexually Transmitted Diseases.

RESUMO

A sífilis, ou lues, é uma doença crônica infecciosa causada pela espiroqueta *Treponema pallidum,* sendo transmitida por contato sexual, hematológico ou placentário. A sífilis não tratada se dissemina em muitos órgãos e compromete o sistema cardiovascular e nervoso, podendo levar o paciente ao óbito. O objetivo deste trabalho foi descrever os principais aspectos da sífilis para o cirurgião-dentista, com o intuito de facilitar sua identificação precoce e conduta. Para tal, foram realizadas buscas na literatura nas bases de dados Pubmed, Embase, Lilacs e Cochrane. Ao final, 6.265 referências foram encontradas e, após a avaliação dos títulos e resumos, 40 artigos foram selecionados para a leitura completa. A sífilis progride tradicionalmente em três estágios. A sífilis primária é marcada pelo cancro, que quando acomete a mucosa oral é mais comum em lábios. As manifestações orais são mais frequentes na sífilis secundária e consistem em placas mucosas brancas, condiloma lata, lesões maculopapulares ou pápulas fendidas. Na sífilis terciária há presença de goma, a qual pode causar perfurações no palato ou alterações na língua, tais como glossite intersticial e glossite luética. A sífilis congênita, por sua vez, afeta significativamente a dentição das crianças. O cirurgião-dentista possui papel essencial na identificação precoce da sífilis e consequente encaminhamento do paciente para atendimento especializado.

Palavras-chave: Sífilis; Treponema pallidum; Dentes de Hutchinson; Patologia Bucal; Infecções Sexualmente Transmissíveis.

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INTRODUCTION

"He who knows syphilis knows medicine". This famous quote by Sir William Osler demonstrates the complexity of diagnosing syphilis in the 19th century, a process that is still challenging in the healthcare field (1). Syphilis, also known as lues, is a chronic infectious disease caused by the spirochete *Treponema pallidum* (2), a bacterium whose only host is the human species (3). It is transmitted mainly through sexual (4), blood, or placental contact (5). The disease represents a major public health issue due to its ability to affect several organs, resulting in dermatological, rheumatological, neurological, and ocular manifestations (6). Besides, syphilis can cause serious complications during pregnancy and facilitate the transmission of Human Immunodeficiency Virus (HIV) (7,8).

Treponema pallidum has been affecting humans for centuries (9). With the emergence of HIV and consequent behavioral changes in society, the incidence of syphilis decreased in the second half of the 20th century. Nevertheless, with the evolution of the management of Acquired Immunodeficiency Syndrome (AIDS) and the resulting false sense of security that sexually transmitted diseases are easily curable, combined with the lack of knowledge of such infections (5), the incidence of syphilis has increased in developed countries since 2000 (10). The World Health Organization (WHO) estimates that, in 2020, there were 7.1 million new cases of syphilis worldwide (11). The disease is widely disseminated in areas with extreme poverty (12) and its prevalence is significantly higher in the group of men who have sex with men (MSM), especially those who are HIV positive (11).

Syphilis is treated with antibiotics, and penicillin is the drug of choice (7). If left untreated, the natural course of the disease traditionally involves three stages, in which there are a variety of oral manifestations (13) that resemble other oral lesions. In addition, syphilic oral lesions are typically asymptomatic (14), making early diagnosis difficult. In view of the recent increase in the incidence of *Treponema pallidum* infection, this narrative review aims to compile the essential aspects of syphilis for the dentist.

MATERIAL AND METHODS

The search strategy combined the MeSH terms "Syphilis," "Syphilis Latent," "Syphilis Congenital" and "Mouth" with their respective entry terms "Syphilis Latent Stage", "Latent Stage Syphilis", "Congenital Syphilis", "Hutchinson's Teeth", "Teeth Hutchinson's", "Oral Cavity", and "Cavity Oral," as well as the free-text terms "Treponema pallidum", "lues", and "diagnosis". The Boolean operators used were "OR" and "AND," and the strategy was applied to the Pubmed, Embase, Lilacs, and Cochrane databases. The inclusion criteria were publications related to the topic, full-text articles available for free through the CAPES Journal Portal, and publications from the last 15 years, in Portuguese, English or Spanish languages. Exclusion criteria were as follows: animal studies, duplicate articles, book chapters, dissertations, and theses. The initial search resulted in 6,265 references, and, after applying the inclusion and exclusion criteria, 40 articles were included in the literature review, as indicated in the flowchart below (Figure 1).

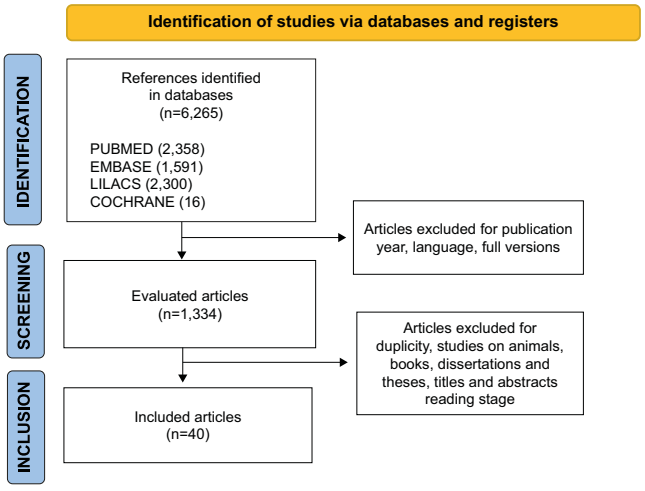

Figure 1 - Flowchart of studies included in the review.

LITERATURE REVIEW

Historical context

Syphilis has been recognized throughout history by different terms: "lues", which means plague in Latin (15), "French disease" (16), and "Neapolitan disease" (17). The first description of syphilis was made by military surgeon Marcello Cumano, at the Battle of Fornovo in 1495, in Italy (9). However, the term "syphilis" has its origins in the book "*Syphilis sive morbus gallicus*" (1), by Girolamo Fracastoro, published in 1530, in which the author describes the disease characteristics (15). The poem tells the story of a shepherd named "Syphilus", the first victim of the disease (16).

It is also believed that the etymology of the term "syphilis" may come from the Greek expression "friend of pigs" (16). The origin of the disease, however, is controversial. While one hypothesis proposes that the bacteria came from the Americas

to Europe aboard Christopher Columbus' ships in 1493, another theory suggests that it was brought with slaves on the sea route between the Iberian Peninsula and Africa (9).

Pathogenesis syphilis

The pathological basis of syphilis is vasculitis (18), and its causative agent is the Gram-negative bacterium *Treponema pallidum* subspecies *pallidum*, a spiral-shaped, mobile, slow-growing bacterium (4,9,18), whose dimensions vary from 0.10 to 0.18 µm in diameter and 6 to 20 µm in length (9). Its virulence factors are not yet fully understood (18). Infection occurs when the bacteria penetrate the mucous membranes directly through fissures in the skin caused by sexual intercourse, or via the placenta and bloodstream, such as direct blood transfusions or sharing needles during injectable drug use (7). Once in the epithelium, these microorganisms multiply and spread throughout the body via the lymphatic and blood vessels (19).

Treponema pallidum is recognized as a stealth pathogen, given that it has low surface antigenicity that allows it to evade the body's adaptive immune responses, thus facilitating its local replication and early dissemination (20). Syphilis has a long incubation period, and it takes approximately three weeks from inoculation until the appearance of the primary lesion (7). Based on the symptoms and time of evolution, syphilis is divided into three stages and a latency period, with distinct clinical and pathological manifestations (21,22), which are represented in Figure 2.

PRIMARY	SECONDARY	TERTIARY	CONGENITAL
■ Lip ■ Gengivae ■ Tonsils ■ Tongue ■ Palate	■ Lip ■ Tongue ■ Palate ■ Buccal mucosa	■ Tongue ■ Palate	■ Tongue ■ Palate ■ Teeth
■ Ulcer (chacre) ■ Single or multiple ■ Lymphadenopathy	■ White mucous patches ■ Condylomata lata ■ Maculopapular lesions ■ Split papules	■ Gumma ■ Interstitial glossitis ■ Luetic glossitis	■ Hutchinson's incisor ■ Mulberry molars ■ High-arched palate ■ Gumma

Figure 2 - Most-affected sites and main oral manifestations of syphilis according to the stage.

Primary syphilis

The classic feature of primary syphilis is the presence of an asymptomatic chancre at the site of inoculation between 3 and 90 days after exposure (4,23), together with associated reactive lymphadenomegaly (24). In the area of initial contact with the bacteria, an isolated papule appears and erodes rapidly, forming a hardened chancre with adjacent erythema (4,13). It is more prevalent in the anogenital region, followed by the oral mucosa (25), where it can affect any area as long as it is inoculated, and it is more frequent on the lips (4.22). In women, the lower lip is more affected, while in men it occurs more on the upper lip, probably due to different sexual practices (24).

Secondary syphilis

In secondary or disseminated syphilis, *Treponema pallidum* affects multiple organs (26) and usually causes systemic symptoms, such as malaise, weight loss, headache, fever, myalgia, and arthralgia. Moreover, the disease is highly transmissible (13). The disseminated stage occurs approximately 4 to 10 weeks after the initial infection and its classic manifestation is the presence of multiple foci of infection in the form of painless macular rashes, 1 to 2 cm in size, reddish or coppery in color, affecting the palms of the hands or soles of the feet (7). It is at this stage that syphilis is usually identified, particularly in women or MSM (7). Symptoms usually appear from the fourth week of the initial infection and may manifest even before the complete resolution of the primary stage (24). Fever, hepatitis, and nephritis may be associated (27).

Head and neck manifestations are more frequent in secondary syphilis, in which 22% of cases show an affected oral mucosa (5). Clinically, the secondary stage manifests in many ways in the oral cavity, including multiple white or reddish mucous patches, usually covered by a fibrinous pseudomembrane (24), condylomata lata (papillary lesions), and split papules (4). The tongue is affected in up to 30% of cases and may show white-pink mucous patches, with or without a so-called serpentine or snail-like

trail (22). If left untreated at this stage, the lesions disappear spontaneously and the latent period of syphilis begins, which can last for several years and may last a lifetime if it does not progress to tertiary syphilis (24). During this period, there are no clinical manifestations, and the infection can only be detected through serological tests (7). In secondary syphilis, the visual system may be affected, and the most frequent alteration is partial or total inflammation of the uveal tract (20,28).

Tertiary syphilis

After the latent phase, approximately 15% to 30% of cases progress to tertiary syphilis (27), which usually involves the central nervous system (tabes dorsalis, general paresis, Argyll Robertson pupils, dementia) and cardiovascular system (ascending aortic aneurysm, left ventricular hypertrophy, congestive heart failure) and can lead to death (20,24). Foci of granulomatous inflammation (gumma) can be found in the skin, mucous membranes, soft tissues, bones, and internal organs (7,27).

In the oral cavity, gumma is most prevalent on the hard palate, and can cause perforation and communication with the nasal cavity; on the tongue, there is an increase in size and formation of a lobulated pattern (interstitial glossitis) or atrophic papillae with deep infection (luetic glossitis) are observed (24).

Congenital syphilis

Syphilis can be vertically transmitted from an infected mother to her fetus, either by transplacental transmission in any trimester or by contact with a maternal lesion during childbirth (29,30). Estimates show that congenital syphilis affects one million pregnant women per year worldwide (31), and usually it manifests three months after childbirth or in the first two years thereafter (30). The most relevant clinical findings for the dentist are the Hutchinson's triad, which consists of Hutchinson's teeth, ocular interstitial keratitis, and deafness associated with the eighth pair of cranial nerves (24). In relation to permanent dentition, *Treponema pallidum* induces an inflammatory reaction that inhibits the ameloblasts of the tooth germ, causing defects in the incisors (screwdriver incisal edge) and molars (mulberry, Fournier or Moon molars), which present globular projections on their occlusal surface (24,32). In congenital syphilis, there is disturbance in the child's growth and skin fissures on the lips are observed, as well as vesiculobullous lesions, maculopapular skin rashes, fever, jaundice, anemia, hepatosplenomegaly, and rhinitis (24).

Diagnosis

The definitive diagnosis of syphilis is based mainly on serological findings. Laboratory tests are of high importance in asymptomatic cases (23). Non-treponemal screening tests, such as Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) are accessible, rapid, but nonspecific. Test positivity tends to decrease in the latent stage of syphilis and is not useful for differentiating reinfection from previous infections (22). If the screening tests are positive, highly specific treponemal tests such as Treponema pallidum Hemagglutination Assay (TPHA) and Fluorescent treponemal antibody absorption (FTA-Abs) are performed. Currently, the Dual Path Platform (DPP®) HIV-Syphilis rapid test is available, based on immunochromatography (33), which identifies antibodies to *Treponema pallidum* in a simple and rapid manner, and is a versatile option for diagnosis in situations without the infrastructure to perform conventional tests (34).

Since highly specific tests for syphilis are permanently positive, they are not appropriate for the diagnosis of a second infection. In these cases, the bacteria need to be detected in biopsy tissue or exudate (23). Syphilis has no specific histological characteristics (35). Histopathological examination usually reveals epithelial hyperplasia (with or without ulceration) and spongiosis with associated exocytosis. However, vasculitis is rarely observed, and spirochetes are not observed (36), since *Treponema pallidum* is not stained by routine tissue preparation (18). Dark-field microscopy is used for this purpose, and the DNA of microorganisms can be detected with nucleic acid amplification tests (20). For the diagnosis of congenital syphilis, not all signs of Hutchinson's triad are always present, and other clinical signs such as frontal bossing, atretic maxilla and high-arched palate are necessary (24).

Given the high prevalence of syphilis, the dentist must be trained to recognize its oral manifestations and favor early identification. A wide variety of clinical conditions can be perceived as syphilis, and include pyogenic granuloma, traumatic ulcerations, atypical aphthous ulcerations, geographic tongue, deep fungal infections, tuberculosis, Crohn's disease, pyostomatitis vegetans, erosive oral lichen planus, drug-related ulcerations, granulomatosis with polyangiitis, and cancer (22). Particularly in situations of simultaneous HIV infection, the natural course of syphilis changes, leading the patient to

early symptomatic neurosyphilis and several unusual presentations, such as vascular involvement (37).

The dentist must perform a detailed anamnesis that addresses the patient's recent sexual history, as well as the presence of systemic symptoms suggestive of syphilis. Early diagnosis is especially important in pregnant women due to the potential sequelae in the newborn. In the face of a suspected case, the professional must reinforce to the patient the importance of adopting preventive practices to interrupt the infectious chain, such as the use of condoms, recommend testing and treatment of the partner, besides referring the patient to specialized medical care to confirm the diagnosis and administer the appropriate treatment.

Treatment

Once detected, syphilis is treated based on the stage, usually with a single dose of long-acting penicillin, which should be maintained above the minimum inhibitory concentration for at least 10 days, since *Treponema pallidum* divides more slowly than most bacteria (20). Alternative therapies are used in patients with allergy to penicillin (38) and include the use of doxycycline, tetracycline, or ceftriaxone (7). The administration schedule and its duration vary according to the stage of the disease and the degree of involvement of the central nervous system (22). At the beginning of treatment, there is a risk of the Jarisch-Herxheimer reaction, a transient immune response that causes fever, chills, headache, myalgia, and exacerbation of existing skin lesions (39). This reaction is more frequent in the early stage of syphilis. It is associated with an elevated VDRL titer and should not be confused with a drug reaction to penicillin (40). In turn, the management of infants and children with congenital syphilis is based on the mother's history and her relationship with the infection and treatment, which includes risk factors for reinfection and a complete physical examination of the child (30), which highlights the importance of prenatal monitoring of pregnant women.

CONCLUSION

Syphilis is a systemic infection caused by the bacterium *Treponema pallidum,* which presents a wide variety of oral manifestations that can occur at any stage of the disease, which makes its identification challenging. Since the incidence of syphilis continues to grow, future research should focus on improving preventive strategies and increasing access to rapid testing in higher-risk populations. The dentist is essential in the process of early diagnosis of syphilis. Through a detailed anamnesis, based on knowledge of numerous clinically similar diseases and serological tests, the professional is able to quickly refer the patient to specialized care.

The authors have no conflict of interest to declare.

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