Infections of the Orofacial Region

Subjects: Others

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The natural flora of the mouth is very diverse. After the large intestine, it has the second highest complexity in terms of microorganisms, including more than 700 microorganisms. Each tissue has specific microbes that are different from adjacent tissues' microbes. Still, these microbes can be displaced under certain conditions, such as the effects of cytotoxic drugs, oral cancer, or epithelial atrophy. The oral flora is divided into two categories, static and transient, which regularly balance with the host and protect against pathogenic microorganisms. The static flora on oral cavity surfaces is known as biofilm that can improve or protect oral health against pathogens, increase the virulence of potentially harmful microorganisms, and reduce the effectiveness of antimicrobial agents. Infections caused by bacteria in the mouth include caries and periodontitis. Microorganisms can attack different parts of the mouth via different mechanisms.

Keywords: oral infections ; orofacial infection ; orofacial microbes

1. Introduction

The tongue is the primary source of microbes in saliva and the major oral site for microbial growth [1]. Some bacterial, viral, and fungal agents can affect the skin and mucous membranes in the orofacial area. These factors can cross natural barriers and cause lesions of varying degrees. Some of them can even be life-threatening. The local and systemic factors determining the microbiota and genetics, as well as the individual factors such as diet, teeth brushing habits, dentures, dental procedures, mouthwashes, medications, etc., can be involved in the occurrence of orofacial infections [2][3][4][5][6][7]. Oral infections can occur under certain conditions, such as poor oral hygiene, antibiotic consumption, trauma, and dry mouth, and can damage the oral cavity. These infections also may spread into the nearby tissues and turn into systemic infections. For example, chronic oral infections are known to be a risk factor for cardiac disease [1].

2. Herpes Simplex Virus

Herpes simplex virus [8] is one of 200 species of the *Herpesviridae* family and belongs to the subfamily *Alphaherpesvirinae*, the genus *Simplexvirus*. Despite differences in host and morphology, this family is thought to be originated from a common ancestor with tailed bacteriophages [9]. These viruses are about 120 to 200 nanometers in diameter. Structurally, they include a circled DNA containing a unique long (UL) segment and a unique short (US) segment (opposite repeats) [9][10]. In addition, they have an icosahedral symmetric capsid, protein coating, and a lipid bilayer cell-like envelope. Genome transcription and replication and the formation of new capsids occur in the host cell's nucleus [10]. These viruses' short reproductive cycle helps them rapidly destroy the host cells [9]. During the infection procedure, the envelope releases the capsid into the host cell's cytoplasm after fusion with its plasma membrane. HSV can attack nerve tissue and multiply there (neuro-virulence). Eighty-three percent identical nucleotides and fifty percent homology in the sequence display a strong association between the two types of herpes virus: HSV-1 and 2 [9].

HSV is also recognized for its latency ability in trigeminal and sacral ganglion nuclei of the ganglia structures [9][11]. HSV fuses to the axon termini to establish latency and moves retrogradely along the sensory fibers (**Figure 1**) [9]. Then, it generates latency-associated transcripts (LATs) that enhance axon regeneration, reduce viral gene expression, and prevent nerve cell apoptosis [12].

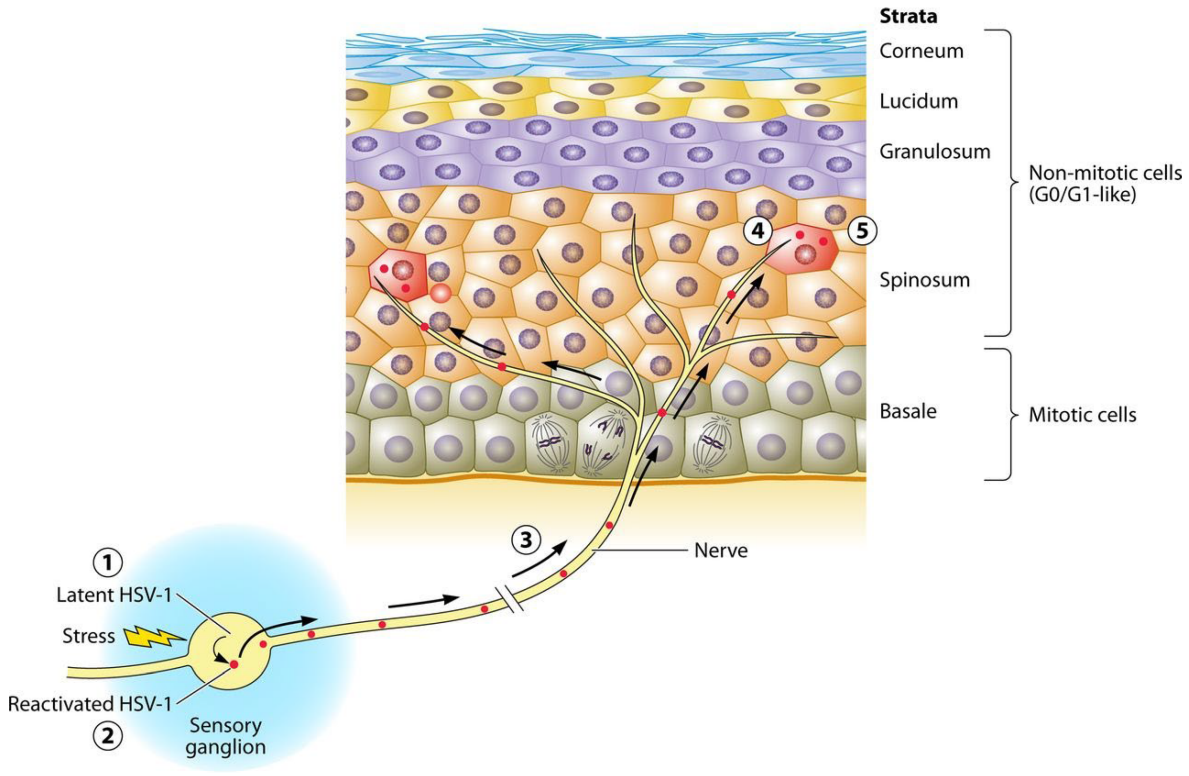

Figure 1. The latent infection of HSV-1 leads to permanent arrest in an G0/G1-like state in the sensory ganglia that will never reenter mitosis ①. During reactivation, virus genes are expressed in cells in the most permissive state ②. Then, reactivated virions travels in axons ③ to termini on the epidermis ④, and then transmitted to the spinosum and granulosum strata layers of the epidermis ⑤ [9].

The disease has no clinical signs at the initial acquisition or during periods of reactivation. However, symptoms occur in the active periods of the disease, following asymptomatic periods, on a rotating basis [13]. Clinical symptoms of the first episode of the disease include headache, fever, muscle aches, and inflammation of the lymph nodes [13]. Then, classic lesions are created that include fluid-filled vesicles that become purulent and dry. Genital herpes includes small blisters resulting in benign ulcers, whereas, in cold sores, several small blisters are aggregated [13]. Other vital clinical signs of common gingivitis include bleeding gums with edema and friable erythematosus. In addition, sores on the buccal mucosa and gums may be yellow based on a red halo. These oral lesions are often associated with anorexia. Symptoms in young children can include drooling, halitosis, and dehydration [13]. Herpetic vitiligo is another manifestation, which is painful, erythematous, and swollen lesions often occur in the distal phalanx of the hand, caused by HSV-1 or HSV-2. This lesion mainly affects the fingers (thumb) and rarely the palm [13]. HSV-1 eczema herpeticum of Kaposi varicelliform eruption is caused by poor immunity due to atopic dermatitis, burns, or topical immunosuppressants. The disease includes vesicular skin lesions [14]. HSV eye keratitis and HSV encephalitis are other complications caused by this virus. Eye involvement can lead to sensitive retinal necrosis, conjunctivitis, blepharitis, or chorioretinitis. Reaching this viral infection to the brain parenchyma leads to extensive hemorrhagic necrosis and vascular occlusion. Encephalitis is the worst outcome that can occur in a healthy person following this infection [14][15].

Because most people with HSV-2 do not have the classic clinical symptoms, genital herpes is more challenging to diagnose than oral herpes and can be confused with related diseases such as fungal infections, lichen planus, atopic dermatitis, and urinary tract diseases. Diagnosis is confirmed by laboratory tests, including polymerase chain reaction (PCR), skin biopsy, immunofluorescence, and virus culture polymerase chain reaction (PCR). Blood and urine cultures determine previous and ongoing infections, respectively. PCR is more sensitive and accurate for diagnosing HSV in mucosal surfaces than vesicular fluid culture. In patients with a history of genital ulcers lacking active lesions, serological diagnostic tests are conducted [16].

Although antiviral drugs, including acyclovir, valaciclovir, famciclovir, and penciclovir, reduce the disease's incidence, duration, and severity, no way exists to remove the virus from the body. Painkillers and topical anesthetic treatments can relieve pain/fever and itching, respectively; however, their efficiency has been controversial [17]. In addition, intravenous infusion of acyclovir is recommended for eczema herpeticum to be limited and prevented from spreading to the eye [15]. Seizure control, fluids management, and intracranial pressure control will improve results in HSV-based eye keratitis [14] [15]. Suppressive therapy, such as corticosteroids, is commonly used to improve pain and tenderness at the onset of symptoms. Oral acyclovir has a positive therapeutic effect on primary and recurrent HSV genital infections [15]. Some

studies have discussed the antiviral activity of some essential oils on the HSV spp. (even acyclovir-resistant strains) through different mechanisms, such as inhibiting cell attachment.

3. Human Papilloma Viruses

Papillomaviruses have a wide genetic diversity. Human papillomavirus (HPV) viruses use human cellular proteins to reproduce and survive [18]. The virus genome consists of open reading frames [19] and long control regions (LCR) to regulate the replication and transcription of primary genes [20]. The main reservoir of HPV is inflamed gums, salivary gland epithelium, and cryptal epithelium of tonsils, oral border, and oropharynx. The most clinically important genus of HPV is the alpha genus of human papillomavirus [18]. In high-risk HPV, placing the virus genome in the host genome breaks the virus genome at the E1 and E2 sites, and losing E2, in turn, causes E6 and E7 to lose control that, inhibits the regular function of p53 and pRb, respectively, and interfere with the cell cycle [21].

HPV infection can be transmitted from the mother's cervix (sexual and non-sexual fomite transmission) and produces clinical or subclinical lesions. Oral HPV lesions include a range of benign oral lesions, lichen planus, fibroma, hyperplastic, papillomatous, verrucous, and carcinoma lesions. Generally, flat, exophytic, or wart-like white lesions in the oral mucosa, exophytic, wart-like, or papillary proliferations can be considered clinical manifestations of HPV [22]. Oral sex is the main transmission root in these diseases, and soft-circumscribed sessile nodular lesions and koilocytosis are some of their pathological and cellular manifestations [23]. The latent location of HPV in the mouth is usually in the gingival pocket because it is the only place where basal cells are in direct contact with the environment [24]. In about one-fourth of patients with periodontal disease in a clinical survey, the gingival samples have been associated with HPV [24].

There are several diagnostic methods for HPV. Immunohistochemical analysis-specific antibodies (e.g., p16INK4A and p16 IHC) and HPV mRNA/DNA-detecting PCR are the sensitive and cost-effective diagnostic methods for HNSCC tumor specimens. However, studies have shown that mRNA tests are the best approach for confirming the diagnosis [25]. Serological biomarker tests cannot be used for detecting HPV infection in the oral cavity. Their examination in oral fluids is useful for identifying and examining the incidence and course of the disease as they are low-cost, non-invasive, and local-specific [26].

Syrjänen discusses that HPV particles only get inactivated at temperatures 75–80 °C [27]. Preventive approaches such as vaccination and routine screening of HPV antibodies in the saliva are among the most effective ways to prevent HPV-associated head and neck diseases. Cold therapy, electrosurgery, surgical resection, laser therapy, and trichloroacetic acid are the usual treatments for papillomas/condyloma, verocroas, and FEH occurred by HPV [18].

4. *Candida albicans*

More than 200 species of the genus Candida are usually non-pathogenic in humans. However, in immunocompromised individuals, *Candida* is the most frequent cause of oral mucosal infections, commonly due to antibiotics and the consequent change in the bacterial microbiota. In addition, suppressing the local or systemic immune system prepares the environment for infection. This group's most common pathogen species is *C. albicans*, which accounts for more than 90% of oral lesions [28]. Morphological control between yeast and hyphae by *C. albicans* is involved in its pathogenesis. *C. albicans* co-adhesion with oral bacteria such as *S. mutans* helps it to colonize, persist, and grow by receiving a carbon supply. Vice versa, *Candida* reduces the bacteria's oxygen stress, promotes better bacteria adhesion, and prepares stimulatory growth factors [29][30].

Pseudomembranous, erythema, hyperplasticity, mucosal irritation, and edema are the symptoms of primary oral candidiasis [31][32]. In more severe cases, hemodynamic instability, positive blood cultures, fever, shock, and tachycardia may occur [31]. *Pseudomembranous Candidiasis* (thrush) is found on the white plaques, buccal mucosa, oropharynx, and junction of the hard and soft palate and is the most common form of candidiasis. Although some patients may experience a sour taste, burning sensation, and bleeding in the affected areas, most patients are asymptomatic [32]. Candidiasis may be hyperplastic or atrophic and occurs in either chronic or acute forms [31][33]. Different types of candidiasis can be asymptomatic or ulcerous [31]. Hyperplastic candidiasis resembles leukoplakia and may involve the labial commissures and become malignant [33]. Its chronic form is challenging to diagnose since the hyphae may hide in any rough surface in the oral cavity, such as papilloma, epithelial dysplasia, and squamous cell carcinoma [33]. Acute atrophic candidiasis is usually iatrogenic (such as antibiotic consumption) and especially common in HIV patients, whereas chronic atrophic candidiasis is iatrogenic mainly due to orthodontic retainers or dentures that do not adequately fit in place [31]. Chronic atrophic candidiasis and inflammatory papillary hyperplasia [34] may also accompany due to iatrogenic candidiasis because of taking biopsies from median rhomboid glossitis, smoking, and inhaled steroids, for instance [31].

Candidiasis suspicion is based on examining mucosal changes, stained smears with Schiff's reagent or KOH, and histopathological biopsies, searching for the hyphae or epithelial parakeratosis with polymorphonuclear leukocytes [35]. Transcribed internal distance sequencing [36] can be used to identify emerging candidate species and the historical course of candidiasis. For the rapid diagnosis of invasive candidiasis, serological biomarkers, including antibodies against mycelium, β-d-glucan (BDG), mannan antigen (Mannan-Ag), and mannan antibodies, are evaluated [37]. Endoscopy is also necessary for esophageal candidiasis suspicion patients [31].

Polyenes and azoles are two types of antifungal drugs [38][39]. Polyenes (with conjugated double bonds) bind to sterols (mainly ergosterols) and change the cell membrane transfer temperature. Then, the leakage of monovalent ions (K^+, Na^+, H^+, and Cl2) and small organic molecules lead to cell death [38]. On the other hand, azole stores α-methylase enosterol to prevent the lanosterol to ergosterol conversion. These topical drugs have no pharmacological systemic side effects since they have no systemic absorption. In cases where topical drugs do not respond, systemic drugs are used [39]. Studies have shown that probiotics may affect the toxicity of *C. albicans*.

5. *Aspergillus*

Aspergillosis genus is the second most common opportunistic fungal infection in humans. *Aspergillus fumigatus* is an air-borne fungal pathogen causing many diseases [40][41]. This pathogen has a saprotrophic mycelial with an efficient spread through asexual spores and a life mostly on decaying organic matter secreting a wide range of enzymes (e.g., amylases, xylanases, pectinases, and elastase) [40].

The main virulence factors of *A. fumigatus* are its cell wall containing polysaccharides (90%) and proteins and the glutotoxin from the epipolythiodioxopiperazines family [40]. Through the pathogenesis of Aspergilloma (noninvasive chronic pulmonary Aspergillosis), *A. fumigatus* hyphae form a biofilm in the extracellular matrix (ECM) with a different cell wall composition and structure [42].

Aspergillus colonization function damages the epithelial cells and upregulation of ECM proteins by disrupting the expression of the ZNF77 transcription factor in bronchial epithelium and causing conidial adhesion. The immune system-survived and metabolically activated conidia grow, germinate, form hyphae, spread by attacking blood vessels, and invade the lung tissue [43]. Aspergillosis is divided into three categories: invasive (nonfulminant and fulminant), noninvasive, and noninvasive destructive. The nonfulminant invasive types are slowly progressive, and the fulminant invasive types are very aggressive. The non-invasive type can be locally destructive but has no tissue invasion and includes Aspergilloma, fungal ball, and Mycetoma [35][44]. Headache, fever, nasal congestion, swelling of the face, purulent or bloody nasal discharge, nasal pain, and epitaxy are the clinical symptoms of *A. rhinosinusitis*. This diagnosis should be considered in people with regular sinusitis or who are resistant to antibiotics. Oral lesions associated with Aspergillosis and other systemic mycoses can be considered dispersed diseases of the lungs. Irregular oral lesions may indicate the spread of an adjacent structure, such as the maxillary sinus, or a significant infection of the oral mucosa [45]. In the first stage of *Aspergillosis*, marginal growth areas appear to contain degraded epithelium and infiltrate fungal hyphae in the connective tissue. In the next stage, the previous lesions change to necrotic gray lesions and spread by attachment to the gums by ulceration and pseudomembrane. Invasion of the arteries is found at the base of these wounds. In the last stage, progressive damage to the alveolar bone and muscles is characterized by histopathological evidence of the penetration of fungal hyphae around the face [46]. Poor outcomes were associated with cases of older age, bone marrow transplantation, high sequential organ failure assessment (SOFA) score, and mechanical ventilation [47].

To diagnose Aspergilloma, chest radiographs are still a suitable imaging technique that shows a round solid body enclosed in a radiolucent crescent in the upper part of the lung (bilateral and multiple). Thin-section chest computed tomography (MDCT), multiple incision (MSCT), spiral computed tomography (CT), and high-resolution CT at the optimal dose are suitable methods for patients at risk of IA. In the early stages of IA analysis, CT lung angiography can show vascular occlusion at the level of a suspected fungal lesion [48].

The standard doses of anti-fungi drugs recommended for treating IA may not be safe or effective for all patients. Then, high doses of drugs are commonly required in severe infectious diseases, treatment of difficult places, and infections caused by *Aspergillus* spp. with increased MIC. Patients with hematological malignancy at risk for IA are also managed by receiving initial prophylaxis or controlling biomarkers without receiving prophylaxis [49]. Oral-delivered Raziol treats CPA. All treatment instructions for the invasive Aspergillosis include using azoles, Amphotericin B (AmB), or echinocandin at appropriate doses with therapeutic evidence.

6. *Actinomyces*

The genus *Actinomyces* spp. belongs to the typical human flora that can be found in the oropharynx, gastrointestinal tract, and urinary tract. It is one of the leading oral bacteria usually identifiable in healthy dental mucosa, dental plaque biofilm, periodontal lesions, and root rot. Actinomycosis resembles malignancy, tuberculosis, or nocardiosis in terms of its continuous and gradual spread [50].

Complete vascularization of mucosal tissues and their replacement by weakly irritated tissue in actinomycetes supports its growth and provides adequate oxygen pressure. In necrotic foci, filamentous “sulfur” granules spread as a “sunburst radiation”. The ends of these granules can form extensions or rosettes due to the adhesion of neutrophils [51]. Cervicofacial clinical symptoms, which may last from 4 days to 1 year before diagnosis, include irregularly painful soft-tissue swelling of the submandibular or perimandibular area and emptying of the sinus ducts with sulfur granules, chewing problems, and recurrent and chronic infection [51]. In about 10% of patients, the bone is involved. Chronic infection can lead to osteomyelitis of the jawbone. Osteomyelitis due to cervicofacial Actinomycosis can spread to the lungs, gastrointestinal tract, tongue, sinuses, middle ear, larynx, ciliary tract, and thyroid gland [52].

The best diagnoses are histological examination and bacterial culture of abscesses or suspected tissue. Staining sulfur granules with hematoxylin–eosin turns them into round basophil masses containing eosinophilic terminal clubs. Prescribing antimicrobial drugs leading to false negative culture results may cause anemia, mild leucocytosis, increased erythrocyte sedimentation rate, and increased C-reactive rutin value. Increased alkaline phosphatase concentrations may be seen in patients with hepatic Actinomycosis [53]. The blood test is a nonspecific diagnostic method for this disease. Imaging features are nonspecific and non-diagnostic in the early stages and may even be related to other inflammatory processes or neoplasms. Although cross-sectional imaging with CT or magnetic resonance imaging (MRI) does not provide accurate or diagnostic information, it can provide accurate anatomical information for sampling. Regional lymphadenopathy is rare in these patients.

Depending on the infection course, the course of antibiotics determines the clinical manifestations and response in Actinomycosis. The treatment is experimental because no similar success has been achieved with any antibiotic. The use of high doses of intravenous antibiotics for 2–6 weeks or 6–12 months orally is the primary treatment [54]. Acute lesions are often treated with tooth extractions, abscess drainage, and antibiotics for 2–3 weeks (penicillin). The penetration of antibiotics into the lesion may be delayed by weak vessels and solid capsules. Surgical interventions such as bone necrosis removal are performed for subacute or chronic voluminous lesions [55].

7. *Streptococcus mutans*

S. mutans lives in the mouth, specifically on dental plaque. Its importance is for involvement in the etiology of dental caries and its possible association with subacute infective endocarditis. Studies have shown that *S. mutans* is a major cause of tooth decay because of its ability to make large amounts of organic acids and activity at low pH compared to other species [56][57][58]. Through pathogenesis, *S. mutans* develop a biofilm starting by attachment of the initial pioneer species followed by colonization, co-adhesion, and co-aggregation of other species. Then, the bacteria produce extracellular polysaccharides, separate from the biofilm surface, and spread in the oral cavity environment [59]. *S. mutans* produces a sticky glucan by the action of glucosyltransferases (GTF) on sucrose that helps bacteria tight binding to the tooth surface. This binding allows bacteria to withstand rapid and frequent environmental fluctuations such as nutrient access, aerobic to anaerobic transfer, and pH changes. *S. mutans* also produces other virulence factors, including glucan-binding (Gbp) proteins and antigenic cell surface protein (PAc). PAc is in contact with salivary glands and plays an essential role in bacterial adhesion to tooth surfaces [60].

Tooth decay, the leading cause of tooth loss, is a multifactorial, infectious, and transmissible disease [61]. According to plaque-specific plaque (SPH) hypotheses, certain Gram-positive acidogenic and aciduric bacteria, including *S. mutans* and *S. obrinus* are typical infective dental plaques causing tooth decay as a biofilm-mediated disease in humans [62]. Environmental conditions such as regular daily sugar intake or salivary dysfunction increase the aciduric/acidogenic oral microbiome. As the lesions spread, the physiological balance between the tooth mineral and the biofilm fluid is disturbed, moving toward demineralization [63].

Caries is diagnosed by visual and tactile dental examination. Alternative methods, including illumination-based methods such as optical coherence tomography [32], near-infrared [46], and fiber-optic technology, are also available [64]. In addition, the quantitative fluorescence light (QLF) devices, categorized by red, blue, and green labels based on the various wavelengths they generate, can be used in the early stages of caries [65]. Another method is an electronic caries monitor

(ECM) that measures the bulk resistance of dental tissue. Material properties such as porosity, contact area, tissue thickness, enamel hydration, and ionic content of tooth fluids determine its electrical conductivity.

First, biofilm management should be considered before tissue removal [66]. Patients are advised to consume less fermentable carbohydrates to correct the environmental pressures responsible for plaque biofilm dysbiosis [67].

8. *Streptococcus sanguinis*

S. sanguinis is a member of the Streptococcus family and a Gram-positive and facultative anaerobe. Similar to other streptococci, *S. sanguinis* divides along a single axis. According to reports, *S.sanguinis* is nonmotile. *S.sanguinis* use several carbohydrate sources to sustain itself. During the eruption of the first teeth of toddlers, *S. sanguinis* colonizes the oral cavity. Streptococcus species, however, have been reported to form biofilm during the first four to eight hours following biofilm formation.

In general, *S. sanguinis* and *S. gordonii* are less acid-tolerant than *S. mutans*, but they contain arginine deiminases, which produce ammonia and provide ATP when exposed to acidic conditions. This system improves the survival and persistence of these organisms. Researchers have found that bacterial uptake and catabolism of specific carbohydrates can affect H_2O_2 and AD production by these commensals [68].

It has been primarily physiological and biochemical characteristics used to identify *S. sanguinis* in the past. Nevertheless, phenotypic identification methods and investigators differed in reliability and reproducibility. Previously, genotypic and phenotypic methods did not accurately identify clinical *S. sanguinis* isolates. To identify *S. sanguinis* and other oral bacteria, other methods, such as PCR with nucleic acid probes, are being investigated. [69].

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