VIRAL AND FUNGAL INFECTIONS OF THE ORAL MUCOSA: PREDISPOSING FACTORS, CLINICAL ASPECTS, DIAGNOSTIC AND MANAGEMENT. REVIEW

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Abstract
Mucous membranes and skin the in the orofacial region are often affected by a diverse spectrum of bacterial, viral, fungal, chlamydial, rickettsial, protozoal, and helminthic infections. Such conditions may clinically appear as small, localized lesions to diffuse and invasive varieties that extend beyond natural barriers, often causing potentially life-threatening complications. Regardless of the prevalence, incidence, and the advancement of treatment strategies, orofacial infections, either local or the manifestations of a generalized infection, may cause significant discomfort and suffering. Thus, the recognition of the clinical presentation of these infections is paramount to their diagnosis, clinical management, and appropriate referral. The following sections describe orofacial manifestations of human herpesvirus and fungal infections.
Keywords: *Viral and fungal infections, oral mucosa, periodontal disease*

Introduction
A critical assessment of clinical signs and symptoms, likelihood of individual and communal predisposition, the past medical, dental and social history, appropriate sampling, and accurate interpretation of the laboratory results are all essential in determining definitive diagnoses and management protocols. Therefore, in this paper, we discuss the types, incidence, predisposing factors, diagnostic algorithms, and management of common orofacial infections of viral origin. **[1]**

Although many viruses can infect the oral cavity, members of the human herpesvirus family cause the most common viral infections with variable clinical presentations.

Additionally, all herpesviruses are neurotropic and have the important property of remaining latent, with the ability to reinfect the host and cause recurrent infection after a variable period of the primary infection.

Human herpesviruses. All herpesviruses are structurally similar, and they infect both humans and animals. A range of different human herpesviruses have been identified, and they are numbered from 1 to 8. Human herpesvirus 1 (also called herpes simplex 1) causes oral and genital herpes (predominantly orofacial).

Human herpesvirus 2 also causes oral and genital herpes simplex; however, genital manifestations are predominant. The primary infection of varicella zoster virus

(human herpesvirus 3) is chicken pox, and the reactivation of the virus results in shingles. Human herpesvirus type 4, also called Epstein-Barr virus, is known to cause infectious mononucleosis, Burkitt's lymphoma, and central nervous system lymphoma in acquired immune deficiency syndrome (AIDS) patients. Oral hairy leukoplakia, first identified in people with HIV disease, is also caused by Epstein-Barr virus.

Individuals infected with cytomegalovirus, the fifth human herpesvirus, exhibits infectious mononucleosis like symptoms. Roseolovirus (human herpesvirus 6) and human herpesvirus 7 cause a similar infection known as roseola infantum or exanthem subitum. Human herpesvirus 8 mainly causes Kaposi's sarcoma and primary effusion lymphoma; thus, it is called Kaposi's sarcoma-associated herpesvirus.[1] The following sections describe orofacial manifestations of human herpesvirus 1 to 3.

1. Herpes simplex infections (human herpesvirus 1 and 2)

1.1. Epidemiology and Predisposing factors

Children between 6 months and 3 years of age are at higher risk to exposure to herpes simplex virus type 1 through direct contact with another individual carrying the virus. Approximately 60% of the population has been infected by the age 14-49 years, and the infected population rises up to 80%-85% by the age of 60 years.[2] Herpes simplex virus type 2 is one of the most common sexually transmitted diseases, and approximately 17% of US adults between 14 and 49 years of age are chronically infected with herpes simplex virus type 2.[3,4] Alarmingly, 95% of herpes simplex virus type 2 seropositive individuals are estimated to be shedding herpes simplex virus type 2 asymptomatically.[5] Recent reports suggested that, in Western countries, the incidence of herpes simplex virus type 1 in children is decreasing and many are exposed to herpes simplex virus type 1 for the first time during their adolescence as a result of an active sexual lifestyle.[6]

Children between 6 months and 3 years are at high risk for herpes simplex virus type 1 exposure, especially through kissing, touching the person's skin, such as pinching a child's cheek; and sharing objects such as silverware, lip balm, or a razor can predispose an individual to be exposed to herpes simplex virus type 1.

The susceptibility to herpes simplex virus type 2 infection is higher among females. In addition, individuals who have had many sex partners, had sex for the first time at a young age, have (or had) another sexually transmitted infection and have a weakened immune

system due to a disease or medication are more prone to be infected with herpes simplex virus type 2. However, greater human immunodeficiency virus (HIV)/herpes simplex virus type 2 coinfection rates were estimated among heterosexuals in sub-Saharan Africa and men

who have sex with men in the Americas.[7-10] Recurrent herpes infections are commonly diagnosed in patients receiving cancer chemotherapy or immunosuppressive drugs to prevent graft rejection after transplantation or with advanced AIDS.[11,12]

1.2. Pathogenesis of herpes simplex type 2 infections

Herpes simplex viruses enter host cells by interaction of their surface glycoproteins (glycoprotein B, C, D, H, and L) with various host cell surface receptors.[13,14]

Alternatively, herpes simplex virus may enter the host cell via endocytosis.[15,16]

Regardless of the method of entry, viral membranes fuse with the host cell membrane to facilitate the entry of viral capsid and accompanying tegument (viral proteins) into the cytoplasm.[17]

Viral capsid binds to the host nuclear pore complex and releases the viral DNA into the host nucleus.[17,18]

Using host RNA-polymerase II, viral DNAs are sequentially transcribed [19,20] in order to encode for proteins required to evade host immunity, replicate viral DNA, synthesize structural components of virions, including tegument, capsid, and other surface proteins.[21,22]

Finally, the virions are carried to the cell surface via vesicles and secreted. These host components include antibodies, natural killer cells, complement proteins, and major histocompatibility complex class I or II molecules.[23,24]

Herpes simplex virus resides within trigeminal nerve ganglia and may reactivate with appropriate triggering factors.[25,26]

Once reactivated, viruses travel along the neurons and develop secondary infection in relevant dermatomes.

1.3. Clinical presentation

Classically, herpes simplex virus type 1 is known to cause infections above the waist, including oral and pharyngeal infection, meningoencephalitis, and dermatitis, whereas herpes simplex virus type 2 causes infections below the waist, such as genital and anal infections.

However, both viruses have been isolated in primary or recurrent infections in the oral, perioral, or genital area as a result of different sexual practices.[11,12]

Primary infection (primary herpetic gingivostomatitis) In most cases of herpes simplex virus infections, patients experience prodromal symptoms such as burning, itching, or tingling sensations of the skin or mucosa for a day or so.[11,12]

Primary herpes simplex virus infection appears with systemic symptoms, which may include fever, headache, malaise, nausea, vomiting, and accompanying lymphadenopathy.[27,28] Usually, herpes simplex virus infections are subclinical or may cause pharyngitis. As a result, it is often misdiagnosed as an upper respiratory tract infection.

Oral lesions appear on the lip or around the mouth, less frequently on the tongue, palatal and buccal mucosae, and the face. The blisters or vesicles erupt as clusters and ooze with a clear to yellowish fluid that may develop into a yellowish crust. These eruptions are extremely painful and break down rapidly and appear as tiny, shallow-grey ulcers on a red base. Subsequently, they become crusted or scabbed and appear drier and become more yellowish in several days. [2]

Primary herpetic gingivostomatitis can also manifest as vesicles and ulcers on the oral mucosa and in marginal gingiva, causing acute generalized marginal gingivitis. The ulcers cause intense erythema in the gingiva and possible bleeding.[11,12] Cervical lymphadenopathy is a common finding in herpes simplex virus infections.[2]

Upon recovery from the clinical infection, the virus could become dormant in trigeminal ganglia. Reactivation of this latent virus can result in recurrent herpes infections.

Reactivation is usually triggered by exposure to cold, sunlight, traumatic events, stress or immune suppression.[11,12]

The most common manifestation of a recurrent herpes simplex virus infection is herpes labialis, which typically appears at the mucocutaneous junction of the lip, often referred to as *"cold sores*" or "*fever blisters*" (Fig. 1).

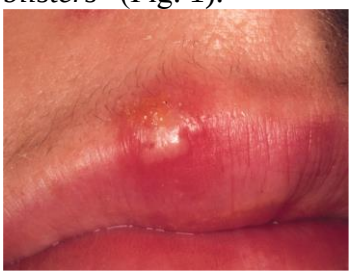

Fig. 1. Herpes labialis on the mucocutaneous junction of the upper lip. Samaranayake [1]

Herpes labialis also exhibits burning or tingling sensations of the site of future blisters. Small fluid-filled semi-translucent blisters appear on the lips and may coalesce to form a large blister. Blisters dry out within several days, resulting in scab formation.[2]

1.4. Diagnosis and management treatment

When the clinical infection is present, diagnosis is made mainly with clinical presentation. However, laboratory tests may be necessary to confirm and to establish the diagnosis of atypical presentations.[29] These include virologic tests in which the presence of the virus is
confirmed by the cytopathic changes in a tissue culture infected with the virus.[11,12] In addition, cytology smears stained with Giemsa or Papanicolaou stain are used to identify the characteristic cytopathic and viral features in the suspected smear.[30]

Immunological tests, such as direct fluorescent assay, detection of viral DNA through polymerase chain reaction (PCR) assays (the test of choice for herpes simplex virus) and serological tests to detect anti-herpes simplex virus antibodies in serum, are commonly used in the diagnosis.[27-33]

The treatment for primary infection is usually palliative. Mild cases of the infection are managed by supportive care, which includes adequate hydration, pain and fever management with analgesics and antipyretics, topical anesthetics, such as viscous lidocaine, or a mixture of liquid Benadryl, milk of magnesia, and carafate to decrease oral pain.[34,35]

Antiviral therapy with acyclovir, valacyclovir and famciclovir are proven to reduce the symptoms if started within 24-48 hours of vesicle eruption.[27,28,36,37]

Recurrent infections in otherwise healthy patients are also treated symptomatically.

However, patients with chronic immune suppression or with severe, painful, or deforming recurrent herpes may require systemic antiviral medications.[38]

Despite multiple attempts made to develop vaccines against herpes simplex virus infections during the last two decades, the success of such trials appears to be minimal and ineffective in either preventing the occurrence or shedding of the virus [39,40]; usage of viral subunits has also raised concern about potentially developing infection, and application of neutralizing antibodies instead has also been under discussion. However, in a recent trial, a can result in recurrent herpes infections.

However, in a recent trial vaccine containing herpes simplex virus 2 glycoprotein D showed superior effect against herpes simplex virus 1–induced genital infections compared with herpes simplex virus 2 infections in the same site.[39-43]

The latter finding encourages one to think that promising vaccines against herpes simplex viruses are likely to become a reality, and the field of novel microbicides against herpes simplex viruses is promising and is likely to generate agents thatcan cure the infection permanently.[44]

2. Human herpesvirus 3 primary infection: Varicella zoster

2. 1. Epidemiology and Predisposing factors

Varicella zoster infection is prevalent worldwide. Prevalence in adults is higher than in children. The occurrence is higher in tropical countries than in other climates. Varicella exhibits classical seasonal fluctuations in temperate climates, with the highest incidence of the
infection occurring in winter and early spring. The seasonal variations are less commonly experienced in tropical areas.[45]

Newborn babies, specially within first 28 days of life, pregnant women who have not been exposed to chicken pox before, and immunocompromised individuals such as those with leukemia or Hodgkin's disease, or those taking immunosuppressive medications,
are at higher risk of developing longer and more serious illness.[46]

Varicella is extremely contagious, and the risk of secondary attack among susceptible household contacts is as high as 90%.[45]

2. 2. Clinical presentation, diagnosis and management treatment

Chicken pox is a benign infection in childhood. It spreads by direct contact with an infected individual, especially with skin

lesions or nasopharyngeal secretions.11,12 Symptoms of the infection usually appear after an incubation period of 10-21 days.
Skin lesions are intensely pruritic and maculopapular in appearance.
The rash rapidly develops into fluid-filled vesicles with an erythematous base (dew drop on a rose petal). Oral lesions, mainly vesicles and ulcers, are similar to herpes simplex virus
infections and commonly seen on the palate, pillars of fauces,
and uvula.[38]
Clinical presentation of the infection is pathognomonic. When symptoms are not present, identification of viral DNA in serum, saliva, or cerebrospinal fluid aids diagnosis.[38] Management of chickenpox is symptomatic, such as adequate hydration, bed rest, and fever
control by paracetamol (aspirin should be avoided). Lukewarm baths and lotions are useful to reduce itching.[46] However, in severe cases, antiviral therapy is recommended.

3. Human herpesvirus 3 reactivation: Herpes zoster

3.1. Epidemiology and Predisposing factors

Herpes zoster (shingles) is a sporadic disease, and the lifetime incidence is estimated to be 10%-20%. Incidence of shingles rises with aging, doubling in each decade past the age of 50 years. In the United States, approximately 50% of persons living until the age of 85 years will develop zoster.[45] There is a 15 times higher incidence of shingles in HIV-infected
patients compared with uninfected, and blacks are one fourth as likely as whites to develop herpes zoster. There is 15% household transmission rate.[47-50] The lifetime risk of herpes zoster is estimated to be at least 32%. Herpes zoster has no seasonal variation and may be reported throughout the year. Patients who have had varicella zoster, those who are older than 50 years, and those who have compromised immune status (eg, HIV infections, diabetes, under steroids or cytotoxics) or are suffering from cancer are at high risk of having shingles. Stress and trauma are also known precipitation factors.[50]

3.2. Clinical features diagnostic and management treatment

The initial symptoms range from pain, tenderness, and paresthesia along the course of the affected nerve. Vesicles appear unilaterally after 3-5 days in the dermatome supplied by the affected nerve. Vesicles have inflamed bases. Herpes zoster can affect the motor nerves occasionally. When facial nerves (geniculate ganglia) are affected, lesions appear unilaterally along the external ear, face, and oral mucosa. Unilateral facial paralysis is not uncommon, causing Ramsey-Hunt syndrome.11,12
Ophthalmic, maxillary, or mandibular branches of the trigeminal nerve can be affected, and this results in painful skin lesions as well as intraoral lesions along the course of the affected branch (Fig 2).

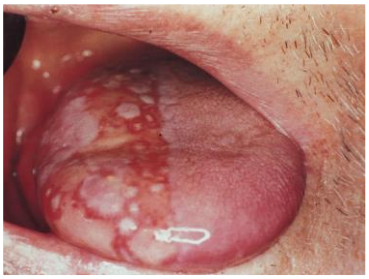

Fig. 2 Herpes zoster of the tongue. Note the unilateral lesion due to reactivation of the infection via lingual branch of the right trigeminal nerve. Samaranayake [1]

Intraoral lesions are intensely painful. [38] Post–herpetic neuralgia may develop as a consequence of herpes zoster due to scarring of the nerve involved during the infection. [11,12] Post–herpetic neuralgia is an intensely painful and debilitating condition that may
last for many months to years.
Diagnosis is based on clinical presentation. Laboratory tests may be necessary for less-typical
presentations. These tests include direct fluorescent antibody staining of varicella

zoster virus–infected cells, the use of PCR to detect varicella zoster virus DNA, and serologic
tests. However, it is difficult to distinguish herpes zoster from varicella zoster by serologic tests.[51] One study showed that the sensitivity and specificity of detecting varicella zoster virus DNA in cells from the base of lesions after they are unroofed by PCR was
95%-100%, whereas immunofluorescent tests in detecting viral antigens were only 82% sensitive and 76% specific.[52] When there is a systemic involvement, PCR assays are used to detect viral DNA in cerebrospinal fluid and blood. It has been recently shown that elevated
ratio of varicella zoster virus antibody level in cerebrospinal fluid to blood is a more sensitive parameter in diagnosing central nervous system involvement of varicella zoster virus.[53]
Antiviral drugs speed healing of the lesions and reduce the duration of severe pain (valacyclovir 1 g three times a day for 7-10 days).
Intravenous acyclovir is required for immunocompromised patients.
Short courses of corticosteroids, such as oral prednisone, are often used to control the inflammatory response associated with severe pain.[54] In addition to antiviral therapy and corticosteroids, post–herpetic neuralgia is treated with gabapentin, tricyclic antidepressants,
opioids, topical capsaicin, and topical lidocaine patches to assist with pain control.[11,12,51]

4. Other oral viral infections

The foregoing describes only the most frequent oral viral infections belonging to the herpes group of viruses. Yet, dentists frequently see patients with an assortment of infections caused by RNA viruses, such as the rhinovirus (common cold virus), influenza virus, coxsackievirus (hand, foot, and mouth disease), and measles and mumps viruses.
These infections may or may not present with oral manifestations, but they are important in the context of infection control aspects of dentistry.
There are new viral infections re-emerging and emerging incessantly in different regions of the world, such as the recent Ebola virus outbreak and Zika virus infection in Africa and South America respectively. Increase in host susceptibility due to poor personal and social hygiene, overcrowding, societal breakdowns (such as wars and civil chaos), poverty, and lack of public health care, and human factors such as sexual and substance abuse activities
can create favorable environments for new and re-emerging viral infections.[56]
Natural mutations of viruses that increase viral virulence (eg, influenza), geographical transfer of viruses to distinct human populations (eg, chicangunya) and viruses crossing the
species-specific barriers (eg severe acute respiratory syndrome, HIV infection, and Ebola) also have a major impact on emerging new infections. Though there is a lack of reports on oral manifestations of the new, re-emerging viral infections, it is still too early
to exclude the potential of oral complications of these diseases.
With emerging new infections as well as isolation of mutant and drug resistant variants of existing viral pathogens, specific and sensitive diagnosis are of paramount importance in managing existing infections and preventing further individual and communal dissemination.
The new era of clinical virology is moving towards highly specific new generation diagnostic tools such as nucleic acid amplification tests, real time quantitative PCRs, next generation sequencing, and mass spectrometry. These technologies not only possess extreme sensitivity and specificity, low detection limits, but also produce fast and automated results facilitating early interventions.[57]

5. COVID-19 from a Dental Perspective

The novel corona virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2),
and the disease it causes, COVID-19 (Coronavirus Disease-2019) have had multi-faceted effects on a number of lives on a global scale both directly and indirectly.

A growing body of evidence suggest that COVID-19 patients experience several oral health problems such as dry mouth, mucosal blistering, mouth rash, lip necrosis, and loss of taste and smell. Minor aphthae associated with SARS-CoV-2 infection. (Fig.3 – Behzad Iranmanesh Int. J. of Dermatology 2020) [58]

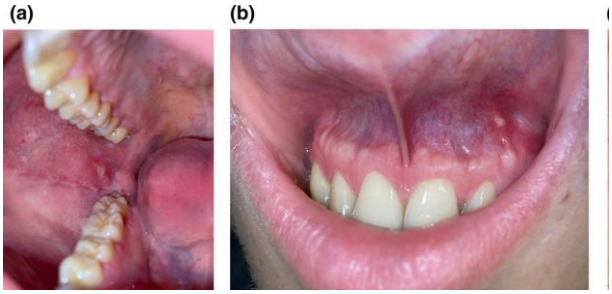

Fig 3. (a) Single ulcer in the right buccal mucosa, with erythematous peripheral rim. (b) Single aphthous ulcer in the superior mucogingival junction. (c) Seven aphthae in the ventral right side of the tongue mucosa. (d) Four clustered aphthae in the right side of the inferior labial mucosa

Periodontal disease (PD), a severe inflammatory gum disease, may worsen the symptoms associated with COVID-19. Routine dental and periodontal treatment may help decrease the symptoms of COVID-19. PD is more prevalent among patients experiencing metabolic diseases such as obesity, diabetes mellitus and cardiovascular risk. Studies have shown that these patients are highly susceptible for SARS-CoV-2 infection.

Pro-inflammatory cytokines and oxidative stress known to contribute to the development of PD and other metabolic diseases are highly elevated among COVID-19 patients.

Periodontal health may help to determine the severity of COVID-19 infection. Dentistry and dental healthcare professionals are particularly susceptible to this virus due to the transferability via the oral cavity and the use of aerosol creating instruments that are ubiquitous in this field. Finally, this review is a valuable resource for the management of oral hygiene and reduction of the severity of infection.

As a profession, dentistry deals with the human oral cavity, the main route for the spread of this disease (sneezing and coughing) [59].

As we learn more about this infection, it is important for dentists and dental practices to update and become as familiar as possible with all aspects of this disease. COVID-19 infection spreads mainly through droplets that remain suspended as an aerosol [59]. Dental procedures create an increased risk for infection to patients, doctors, and staff by producing aerosols and the presence of saliva.

Dental practices should have procedures in place for the prevention of transmission of biological agents. “However, the procedures adopted routinely to date have not been specifically designed for the prevention of pathogens transmissible by aerosol.

Therefore, there are currently no specific guidelines for the protection of dentists against SARS-CoV-2.”

In addition, there are no specific procedures that are in place to prevent transmission by aerosol, so extra precautions must be taken to help prevent the spread of COVID-19 [59].

Fortunately, the latest statistics show that only 0.9% of dentists surveyed (N = 2195) had
contracted COVID-19 infection.

Periodontal bacteria dissemination into the lower respiratory tract may create favorable conditions for severe COVID-19 lung infection. Once lung tissues are colonized, cells that survive persistent bacterial

infection can undergo permanent damage and accelerated cellular senescence.[59]
Consequently, several morphological and functional features of senescent lung cells facilitate SARSCoV- 2 replication. The higher risk for severe SARS-CoV-2 infection, the virus that causes COVID-19, and death in older patients has generated the question whether basic aging mechanisms could be implicated in such susceptibility. [60]
Finally, we highlight the role of saliva as a reservoir for both pathogenic bacteria and SARS-CoV-2. Therefore, the identification of active severe periodontitis can be an opportune and valid clinical parameter for risk stratification of old patients with COVID-19.

6. Conclusions

Global pandemics are still a major concern in health care and economic setups, and emergence and re-emergence of infections is not a new phenomenon.
Early detection of the infection and identification of the pathogen are essential in mitigating oral and/or general infections in humans and animals.
When determining the management of these infections, multifaceted approaches must be followed in identifying all aspects that confer antimicrobial resistance, immune evasion profiles, potential mutations, and genotypic disparities.
Emerging novel technologies that are currently in the conceptual and optimizing and launching stages, as well as existing technologies that are being progressively improved, are likely to assist the infection management team to identify and treat infectious
diseases. However, implementation of such techniques for routine practices remains unrealistic due to lack of funding, resources, and technical expertise.
The importance of proper training of oral and general clinicians and diagnostic microbiologists in all aspects of the management of infections of interest must be routinely conducted.
For instance, oral clinicians need to be equipped with up-to- date knowledge of the clinical pictures of new infections, approaches in accurate identification of orally limited infections vs oral manifestations of underlying systemic diseases.
This review focuses and on how the dissemination of periodontal bacteria into the lungs could aggravate age-related senescent cell accumulation and facilitate more efficient SARS-CoV-2 cell attachment and replication. We also consider how periodontal bacteria-induced premature senescence could influence the course of COVID-19 lung infection.
Management protocols of complicated infections, such as those manifesting extraoral involvement or an immunocompromised patient, must be determined by a multidisciplinary team that includes oral clinicians, medical/surgical practitioners, microbiologists/pathologists and other case-specific specialities.

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