# Infections of the Oral Mucosa and Immune Responses

10

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## 10.1 Introduction

The British Dental Health Foundation, a charity-promoting oral health, has reported that only one in six people realises that gum disease may increase their risk of stroke and diabetes (http://www.dentalhealth.org/). An extensive report by the Surgeon General of the United States in 2000 clearly enunciated the link between oral and general health and set out a framework for action, https://www.nidcr.nih.gov/DataStatistics/SurgeonGeneral/Report/ExecutiveSummary.htm. In a large cross-sectional study of over 17,000 men and women a strong association was seen between the presence of oral disease and systemic inflammation and a history of cardiovascular diseases [1]. Worldwide there are considerable inequalities in oral healthcare provision that has a deleterious effect on general health and well-being [2, 3].

The media, both print and electronic, emphasise the importance of health and fitness and oral healthcare is part of that message—and yet in 2012 at the London Olympics 18% of the ELITE athletes said that oral discomfort has seriously affected their performance and almost half of the athletes had not seen a dentist in the last year [4]. The consequences of a high-carbohydrate diet, often part of an athletes training programme, may lead to dental decay and gum disease and the inflammation that accompanies these changes in the homeostasis of the oral cavity has serious and now well-documented effects to general health and well-being.

A recent report of the Joint European Federation of Periodontology and American Academy of Periodontology (EFP/AAP) [5] demonstrated the link between chronic inflammatory states and the onset of diabetes. Other systemic health risks from chronic periodontitis include atherosclerosis, adverse pregnancy outcomes, rheumatoid arthritis, aspirational pneumonia and cancer [6–12]. Head and neck cancers are said to be the fastest growing group of tumours, representing 3% of all cancers in the USA [13], https://www.cancer.gov/research/progress/snapshots/head-and-neck.

The oral cavity is a complex biological environment protected by one of the most sophisticated and important fluids in the body, saliva, which is actively secreted into the mouth. This is a unique body cavity due to the presence of hard tissue (teeth) which is abutted with a mucosal epithelium. This junction, at the gingival margin, allows for access of substances and cells from the systemic circulation into the gingival crevicular fluid and has a considerable effect on the defence of the oral mucosa and development of disease (Chap. 7).

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The *mucosal immune system* contributes to the protection of the oral cavity (see Chaps. 4 and 5) through both innate and adaptive immune functions. Despite an enormous antigenic challenge, the oral mucosa in healthy individuals rarely shows signs of inflammatory responses and is generally regarded as a tolerogenic environment.

Oral pathologies can be driven by infections and/or by dysregulation of homeostasis and many pathologies reflect a contribution of the immune system in either resolution of disease or exaggerated host responses that drive pathology. Failures of the immune system can also contribute to disease through immunodeficiency, where the immune system either fails to recognise a pathogen or is defective in its response. Hypersensitivity, an overreaction to innocuous materials and autoimmunity and the development of immune responses to self-antigen have all been shown to contribute to oral mucosal diseases.

The oral cavity is subject to infections by bacteria, viruses and fungi (Fig. 10.1). Some of the organisms are part of the normal oral flora but become pathogenic due to loss of homeostatic regulation in the tissues. Some parasitic infections also induce oral manifestation but since these are rare they will not be discussed [14].

Two of the most common diseases, caries and periodontal disease, result in damage and loss of the hard tissues of the oral cavity (teeth and bone). An immune response to the antigens of cariogenic organisms can protect against dental caries and the potential for the development of a caries vaccine has been investigated over many decades. In contrast, the host response to periodontal pathogens contributes to pathology. The clinical management of these two diseases will not be discussed.

### 10.1.1 Bacterial Infections

*Dental caries* is one of the most common diseases of humans [15] and recent papers have presented evidence of the disease in prehistory [16–18]. Increased consumption of refined sugars has resulted in an increased rate of caries, and in developing countries the lesions often go untreated due to poverty and lack of provision of oral healthcare.

The major causative organism for dental caries in humans is *Streptococcus mutans.* This highly acidogenic organism is usually found in low numbers where caries is absent. However, in the presence of caries there is an abundance of *Strep. mutans*. Acid production, through fermentation of dietary carbohydrates, erodes the enamel and dentine resulting in carious lesions.

Although *caries* is a disease of the hard tissues, the capacity for its resolution and indeed prevention is dependent on the gingival mucosa and the passage of specific antibodies from the serum into the gingival crevicular fluid. Many vaccine studies have been carried out in animal models that demonstrate that protection from caries can be achieved when IgG antibodies specific for *S. mutans* antigens reach the gingival margin by serum transudation. A selection of early studies is outlined below.

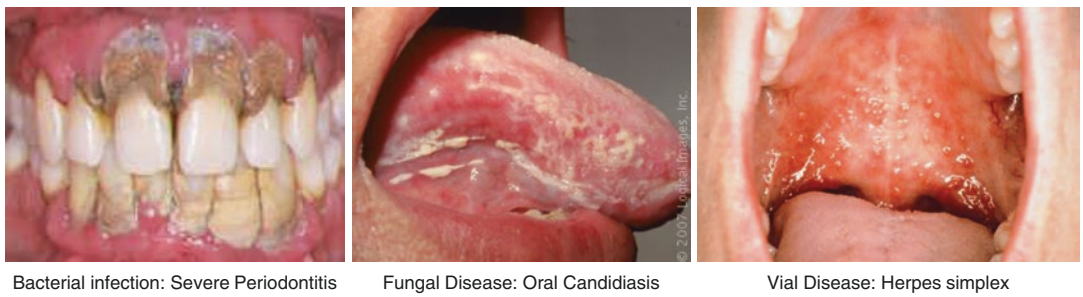


**Fig. 10.1** Common infections of the oral cavity

*S. mutans* has two major antigenic proteins which have been shown to be highly immunogenic: glucosyltransferase (GTF) and the surface adhesion streptococcal antigen I/II (SAI/II). The characterisation of SAI/II [19] led to studies in experimental vaccine design based on SAI/II [20, 21] where protection from caries was established to be due to the induction of IgG antibodies which gained access to the tooth surface through the gingival margin [22, 23]. Passive immunisation studies in rhesus macaques had shown that antibodies applied to the gingival margin could protect against colonisation with *S. mutans* [24]. Observations in human subjects established that the presence of IgG anti SAI/II in serum correlated with low caries incidence [25–27]. Monoclonal antibodies to *Strep. mutans* antigens were later developed and used in passive immunisation studies in both non-human primates and in human clinical trials [28–30]. Passive immunisation using monoclonal antibodies showed that recolonisation was prevented over a period of about 18 months [29, 31–33]. Glucosyltransferase (Gtf) vaccine candidates have been investigated in a phase I clinical trial [34] and induced salivary IgA antibodies which also reduced recolonisation.

In more recent animal model studies nasal adjuvants have been used to enhance the immunogenicity of anti-caries DNA vaccine candidates [35]. Sublingual immunisation with a recombinant phosphate-binding protein (PstP) derived from *Strep. mutans* and administered with a mucosal adjuvant resulted in decreased colonisation and increased IgA antibody-secreting cells in draining lymph nodes in a rodent model [36].

These tools have enormous potential for reenergising the dental caries vaccine field.

Poor oral hygiene can lead to the accumulation of plaque and the development of gingivitis and while this is reversible in some patients it can become a chronic inflammation. Chronic marginal gingivitis (CMG) is the most common form of the inflammatory response to plaque constituents, which include bacterial toxins and antigens.

*Periodontal disease* (PD) is a destructive chronic inflammatory disease of the connective tissues and bone supporting the teeth and is a major source of tooth loss in adults. It occurs when there is irreversible damage to the periodontium that includes loss of collagen fibres in the periodontal ligament, deepening of the periodontal pocket and bone resorption. There are many different types of periodontal disease, some of which are caused by or exacerbated by systemic diseases. The most common form of adult periodontal disease is known as chronic inflammatory periodontal disease (CIPD).

Periodontitis is the result of a dramatic change from a symbiotic community of mostly facultative organisms to a *dysbiotic* community consisting of anaerobic organisms that have evolved to thrive in an inflammatory environment including the acquisition of numerous virulence factors [37, 38]. Microbial *dysbiosis* is defined as a reduction in the number of symbiotic organisms and/or an increase of pathogenic species that have an effect on both the innate and adaptive immune responses [39].

Recent research has built on the knowledge that certain "keystone" organisms have a disproportionate effect on their environment relative to their abundance [40]. *P. gingivalis* is an example of a *pathobiont*, an organism that co-operates with others to remodel its microenvironment into a dysbiotic and disease-provoking microbiota. These new communities can subvert the normally tolerogenic immune system to maintain an inflammatory environment that promotes their survival in the face of a robust immune response [40–42]. However, dysbiosis alone does not always lead to periodontitis. Other risk factors such as genetic susceptibility [43], stress and behaviours such as smoking and diet are important in precipitating disease [44, 45].

The innate immune response to the periodontal organisms includes an increased influx of neutrophils into the periodontal pockets to maintain homeostasis [46, 47]. Individuals with defects in neutrophil function are highly susceptible to periodontal disease [48–50]. However, the effect of the *pathobiont* is to hyperactivate these cells inducing the overproduction of toxic substances and proteolytic enzymes that can initiate tissue destruction [47, 51–53].

In response to infection, macrophages produce pro-inflammatory cytokines, such as IL-1β and TNFα. If these cytokines are produced in high concentrations or for prolonged periods they can induce the production of other inflammatory mediators including IL-6 and prostaglandin E2(PGE2) and metalloproteinases (MMPs). Both IL-1β and TNFα induce bone resorption and inhibit bone formation.

In generalised aggressive periodontitis, a higher IL-1β/IL-10 ratio was observed compared to healthy subjects, suggesting an imbalance between pro- and anti-inflammatory cytokines [54]. In some studies, periodontal therapy was shown to decrease IL-1β levels in GCF while increasing IL-10 [55]. IL-10 is an important anti-inflammatory cytokine that has been shown to suppress MMPs and stimulate an inhibitor of bone resorption (osteoprotegerin). Studies of IL-10 knockout mice demonstrated an increased susceptibility to bone destruction induced by *P. gingivalis* infection [56, 57].

The *complement cascade* is an important mechanism for controlling bacterial infection. Subversion of the cascade can be affected by the gingipains, kaylysins and interpain-A, produced in concert by *P. gingivalis, T. forsythia, T. dentolytica* and *P. intermedia.* The mechanism of action is through interruption of the C5aR-TLR2 signalling cascade and the degradation of C5b, thereby preventing the formation of the membrane attack complex which should destroy invading bacteria [58–60].

Human β defensins are also inhibited in periodontal disease [61], when the gingival epithelium response to *Fusobacterium nucleatum* is subverted by *T. dentolytica* which blocks defensin production. *P. gingivalis* is also capable of degrading antimicrobial peptides (reviewed in [42]).

The adaptive immune response is also important in periodontitis, and antibody responses are readily demonstrated to many of the virulence factors of the keystone pathogens including gingipains (Table 10.1). In experiments, like those carried out for caries vaccines, monoclonal antibodies to *P. gingivalis* were developed and used both in animal models and human clinical trials [62–64]. More recently a therapeutic experimental vaccine demonstrated that IgG1 antibodies protect against experimental periodontitis in mice [65]. Immune responses have also been demonstrated to microbial and human heat-shock proteins [66]. Responses to these chaperone molecules have also been implicated in the immunopathogenesis of ulcerative diseases such as recurrent aphthous stomatitis (RAS) and Behçet's disease (see below).

**Table 10.1** Balance between some beneficial and harmful host defences in periodontal disease

| Periodontal disease | |
|---|---|
| Complex interplay between bacterial species and host defences | |
| Beneficial effects | Harmful effects |
| • IgG ↑ phagocytosis of bacteria<br>• IgA ↓ bacterial adherence | • Ag/Ab complexes: hypersensitivity—attract leucocytes—release proteases—tissue damage |
| • Complement: activated by endotoxin—initiates inflammatory process—recruits neutrophils | • Complement: could induce hypersensitivity |
| • Cytokines: IL-12 recruits immune cells<br>• Phagocytes: destroy bacteria<br>• T cells: help produce antibody | • Cytokines: too much pro-inflammatory cytokine secretion contributes to tissue damage, e.g. osteoclast-activating factor |
| • B cell: produce antibodies against perio-organisms | • Phagocytes: release proteases—tissue damage |

T cells also contribute to PD mainly through the production of cytokines that support antibody production which are prevalent in chronic disease [67, 68]. Both regulatory T cells ($T_{regs}$) and Th17 cells have been shown to be present in periodontal lesions [69].

There is increasing evidence that the presence of IL-17 (produced by both Th17 cells and other cells) in human PD lesions is associated with disease severity. Several animal studies indicate the potential role of Th17 cells in gingival inflammation and bone destruction in PD [70, 71].

This association of *Th17 cells* with chronic inflammation and dysregulation of homeostasis

is a common feature of other oral mucosal diseases described in chapter 11 and its role in oral immunity and shaping of the oral microbiome was recently reviewed [72].

Periodontitis can present without any associated disease but is frequently a major component of systemic disorders such as acquired immunodeficiency disease (AIDS), leukaemia, Crohn's disease, diabetes mellitus, Down syndrome, sarcoidosis and syndromes associated with polymorphonuclear leucocyte defects (Chédiak-Higashi syndrome, agranulocytosis and cyclic neutropenia). Periodontitis can also contribute to systemic disorders and has been found to be an etiological factor in several important diseases including infective endocarditis, pulmonary and brain abscesses and adverse pregnancy outcomes [73–75]. In a recent review, the overlap between the inflammatory processes in PD and in cancer was outlined with respect to the function of chemokines. The main function of these molecules is the recruitment of immune cells into sites of infection and inflammation, but they also have the capacity to prolong inflammatory processes which can exacerbate disease progression including the development of cancer [76].

In a recent study by the Ebersole group, the transcriptome of the B cell compartment was investigated in a non-human primate model of natural periodontal disease and in the healthy gingiva of aging humans. This study revealed complex changes in the expression of genes involved in antigen-dependent activation and proliferation, T cell interaction and maturation of B cells both in adult periodontitis and in aged non-human primates. In healthy aging, gingival homeostasis is maintained by adaptive B cell responses which modulate tissue-destructive gene expression. These functions are lost in periodontitis resulting in immune dysfunction and enhanced inflammation [77].

In an extensive review of the research into the immunobiology of periodontal disease, over the last 40 years, it has been suggested that the transition point between health and disease might be the new frontier for oral biology research [78].

### 10.1.2 Oral Manifestations of Other Bacterial Infections

The barrier function of the oral epithelium, the normal oral flora and the innate and adaptive immune defence mechanisms of the oral cavity make infection by pathogenic bacteria a rare event. The antimicrobial components of the saliva and the desquamation of the epithelium limit colonisation by pathogens.

Some organisms evade the immune system by becoming coated with host proteins that make them less susceptible to neutralising antibodies as is thought to be the case of *T. pallidum* (syphilis). While other organisms have evolved mechanisms that either evade or subvert immune responses such as the changes in antigen serotype expression seen in *Strep. pneumoniae*.

Intracellular pathogens such as *Mycobacterium leprae*, although a very rare condition, illustrate a classic example of immune subversion. Two clinical forms of disease are seen that result in very different patterns of immune activity. In *tuberculoid leprosy* the immune response shows strong Th1 responses and activated macrophages control but do not eliminate the infection. Tuberculoid lesions contain granulomas and inflammation is local, causing only local effects such as peripheral nerve damage. Normal immunoglobulin levels and T cell responses to *M. leprae* antigens are seen and the disease has low infectivity (Table 10.2).

In contrast, *lepromatous leprosy* shows a profound suppression of cell-mediated immunity, leading to anergy, and there is a significant shift from a Th1 cytokine profile (supporting macrophage activation and T cell cytotoxicity) to a Th2 profile. The Th2 cytokines include IL-4 which is thought to inhibit bactericidal activity in macrophages. The mechanism might be like that seen in *Mycobacterial tuberculosis* infection where the organism is taken up by macrophages but the fusion of the phagosome and lysosome is prevented, thus avoiding the bactericidal actions of the lysosomal contents.

In *lepromatous leprosy*, *M. leprae* shows high growth rates in macrophages (suggesting the failure of the phagolysosomal killing of the organ-

**Table 10.2** Granulomatous infections

| |
|---|
| • **Actinomycosis** |
| – Endogenous polymicrobial infections |
| – Submandibular swelling |
| – Chronic suppuration—multiple sinuses |
| – "Sulphur" granules |
| • **Syphilis** |
| – Primary: chancre |
| – Secondary: snail-track ulcers, mucous patches |
| – Tertiary: gumma, lingual leukoplakia |
| – Congenital: dental anomalies; "dished face" |
| • **Tuberculosis**[a] |
| – Oral usually secondary to pulmonary |
| – Painless, chronic lingual ulcer |
| • **Leprosy**[a] |
| – Oral lesions in lepromatous type |
| – Secondary to nasal involvement |
| – Nodular masses palate and anterior maxilla |

Adapted from Soames and Southam: Oral Pathology 4th Edition
[a]Intracellular infections

ism) and the infection becomes disseminated with diffuse nerve damage. Hypergammaglobulinemia is observed, but there is a poor or absent T cell response to *M. leprae* antigens. This form of the disease is highly infectious. Oral lesions occur almost exclusively in the lepromatous form of the disease and are reported in about 50% of cases. Patients present with inflammatory masses that tend to ulcerate and resolve with fibrosis. The hard and soft palate, anterior maxilla and tongue are most frequently affected. The oral lesions are usually secondary to nasal involvement [79].

## 10.1.3 Viral Infections

There are several families of viruses which cause disease in the oral cavity or have oral manifestations following systemic infection (Table 10.3).

*Picornaviruses*, such as *coxsackie A* and *enterovirus 71*, have been associated with hand, foot and mouth disease which causes blistering in the mouth and on the hands and feet of children. While this disease is not usually severe, there have been reports of neurological complications and fatalities when enterovirus 71 is involved. Several serotypes of coxsackie virus (particularly serotypes 1–10, 16 and 22) have also been associated with herpangina, where an oropharyngitis results in oral vesicle which breaks down into small ulcers.

**Table 10.3** Virus infections with oral mucosal presentations

| Virus | Disease |
|---|---|
| Herpes simplex(HSV1 and 2) | Herpetic stomatitis (primary/recurrent) |
| Varicella zoster | Chickenpox/shingles |
| Coxsackie A | Herpangina; hand, foot and mouth disease |
| Epstein Barr | Infectious mononucleosis; hairy leukoplakia |
| Paramyxovirus | Measles; mumps |
| Human papilloma virus | Viral warts; epithelial hyperplasia |
| Cytomegalovirus | Associated with HIV infection |
| HIV | Necrotising periodontal disease; Kaposi sarcoma; candidiasis |

### 10.1.3.1 Herpesviruses

There are eight known human *herpesviruses* with most well known being the herpes simplex viruses (HSV). The two types of *HSV* differ in their serological, biological and clinical presentation. Most commonly type 1 is associated with skin and oral epithelium and has a pattern of recurrence due to reactivation of latent virus from the trigeminal sensory ganglion. Primary infections with HSV-1 are sometimes asymptomatic, but can cause pharyngitis, tonsillitis or herpetic gingivostomatitis. In some patients, progression results in a widespread gingivitis which can be erythematous and oedematous. Vesicles form which can ulcerate and become secondarily infected.

These infections usually heal within 2–3 weeks but during this time the virus has been transported to nerve cells of the oral cavity where they remain latent, often in the trigeminal ganglion, until reactivated. In secondary infection, *herpes simplex labialis* ("cold sore") results from viral migration from the latently infected neurons to keratinocytes where it replicates. Visible lesions recur at the same site.

Inflammatory responses, and papule and vesicle formation, result from the death of infected keratinocytes while neutralising antibody production, and the release of IFNγ from $CD4^+$ and

$CD8^+$ T cells as well as cytotoxic killing of infected cells play a role in limiting the spread of infection and in resolving lesions [80].

HSV-1 has been implicated in the immunopathogenesis of *Behçet's disease* (BD) as it has been isolated from saliva, peripheral blood leukocytes and genital ulcers in these patients. In a mouse model, immunisation with HSV gave rise to BD-like symptoms that were improved with antiviral treatments [81]. However, isolation of HSV is inconsistent and antiviral therapy failed to alleviate BD symptoms. It has been suggested that altered immune responses to HSV in BD compared to healthy individuals may allow persistence of the infection [82, 83].

HSV type 2 is less common and is a sexually transmitted infection; however, changes in sexual habits have resulted in increased oral infections. HSV-2 also has a pattern of latency.

*Latency is an immune evasion strategy*; the epithelial infection is controlled by the immune response; however, the virus that has migrated to the sensory neurons is quiescent and produces few viral peptides. This along with low expression of MHC I in the neurons makes recognition by cytotoxic cells difficult and results in survival of virus and latent infection.

Reactivation most commonly occurs due to a variety of stressors which impair host defences. In immunocompetent individuals, the lesions are self-limiting due to the induction of both specific neutralising antibodies and $CD8^+$ cytotoxic T cell responses which can suppress reactivation [84, 85]. In immunocompromised patients, these recurrences can be intractable and severe.

Chickenpox and herpes zoster (shingles) are caused by *varicella zoster virus* (VSV/HHV-3). Chickenpox frequently presents first in the oral mucosa as small ulcers, followed by the characteristic skin lesions. Like HSV, there is a latent phase, and while reactivation is uncommon it is more severe and causes a painful neuralgia. The location is usually on the trunk but can also occur in the oral mucosa and the eye. Reactivation usually occurs in response to a variety of stressors which have induced suppression of host defence mechanisms.

Other herpesvirus infections with oral presentations include Epstein–Barr virus (EBV/HHV-4) and cytomegalovirus (CMV/HHV-5) and frequently involve enlargement of the lymph nodes and/or salivary glands.

CMV productively infects several types of lymphocytes and has a latent phase in macrophages. CMV has been isolated from periodontal pockets and from other oral mucosal lesions but there is little evidence of cause and effect, other than the presence of infected cells in inflammatory infiltrates. While this virus does not usually cause disease in immunocompetent individuals it is an important opportunistic pathogen in immunocompromised hosts such as AIDS patients and organ-transplant recipients.

CMV escapes immune control by producing four proteins that downregulate MHC class I expression on infected cells so that no viral peptides can be expressed on the cell surface for recognition by cytotoxic cells. The virus also produces a homologue of MHC-I molecules that inhibit the activation of NK cells which under normal circumstances would recognise the loss of the MHC-I and kill the infected cell.

Many people become infected with *Epstein–Barr virus (EBV)* in childhood and show no symptoms of primary infection. A primary infection with EBV later in life is the causative agent of infectious mononucleosis and is transmitted in saliva. Lymph node enlargement occurs and inflammation and ulceration of the oral mucosa at the junction of the hard and soft palates is a frequent presentation.

However, of greater significance is the association of EBV with Burkitt's lymphoma. EBV was the first virus to be shown to have a clear relationship to cancer. This B cell lymphoma is endemic in equatorial Africa and accounts for more than 50% of malignant diseases in children. While the disease tends to be multifocal, in Africa, a jaw tumour is the predominant feature in more than half of the cases.

EBV is also associated with hairy leukoplakia and has been detected in oral squamous cell carcinoma, and there is some evidence of involvement in some types of periodontal disease, but this might be coincidental with lymphocyte infiltration of infected B cells [86].

In other oral diseases EBV shedding has been demonstrated in the saliva of both RAS and Behçet's disease patients [87]. It was suggested

that this might reflect a difference in the expression of TLRs and a dysregulation of the oral microbiota in BD and RAS [88, 89].

The remaining HHVs, namely HHV-6, -7 and -8, are the most recently described human herpesviruses. HHV-6 and -7 appear to be closely related to CMV and both cause childhood disease (HHV-6-exanthema subitum) and both are detectable in saliva. HHV-7 is thought to cause complications in transplant patients due to immune suppression. The target cell for HHV-7 is thought to be $CD4^+$T cells.

HHV-8 is considered the primary etiological agent of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's disease. KS is endemic in Uganda where 50% of the population are seropositive compared to less than 5% in the USA and Northern Europe. In non-endemic regions, infection with HIV is an important risk factor for the development of KS and HIV-1 infection was associated with an increased prevalence of infection with HHV-8 [90, 91].

#### 10.1.3.2 Papilloma Virus

Human papilloma virus (HPV) has been implicated as a causative agent in several types of cancer and an association is thought to exist with oral cancer, particularly nasopharyngeal carcinomas [92–94] and salivary gland tumours [92]. Focal hyperplasia has been associated with viruses that seem to be restricted to the oral cavity, namely, HPV-13 and HPV-32.

HPV-16 (and 18) has a known association with invasive cervical carcinoma with HPV-16 detected in 50% of all cervical cancers in a study carried out in the USA [95]. The effectiveness of the HPV vaccine in reducing cervical cancer has been one of the great success stories of vaccine discovery and the potential for preventing oropharyngeal cancers is yet to be tested.

#### 10.1.3.3 HIV

By far the most investigated virus in the last 30 years is the human immunodeficiency virus (HIV) and the catastrophic failure of the immune response, due to loss of $CD4^+$T cells, leads to a variety of oral lesions outlined in Table 10.4 which can be regarded as opportunistic infections in the absence of a robust immune response. In some respects, these might be regarded as a historical association as the success of highly active antiretroviral therapy has reduced the incidence of these oral manifestations in large areas of the world (but by no means all).

Hairy leukoplakia (EBV infection) and pseudomembranous candidiasis are the most frequent oral manifestations of HIV (Table 10.4 and Fig. 10.2). The presence of these conditions

**Table 10.4** Oral lesions of HIV infection

| Group 1: major associations | Group II: less common associations | Group III: possible associations |
|---|---|---|
| **Candidiasis:** | **Atypical oropharyngeal ulceration** | **Bacterial infections (not gingivitis/perio)** |
| Erythematous | | |
| Hyperplastic | | |
| Pseudomembranous | | |
| **Hairy leukoplakia (EBV)** | **Idiopathic thrombocytopenic purpura** | **Fungal infections (not candidiasis)** |
| **HIV-associated periodontal disease** | **Salivary gland disorders** | **Melanotic hyperpigmentation** |
| HIV-gingivitis | Dry mouth, decreased flow rates | |
| Necrotising ulcerative gingivitis | Swelling of the major glands | |
| HIV-periodontitis | | |
| Necrotising stomatitis | | |
| **Kaposi sarcoma (HHV8)** | **Viral infections (Non-EBV)** | **Neurological disturbances** |
| | Cytomegalovirus | Facial palsy |
| | Herpes simplex virus | Trigeminal neuralgia |
| | Human papilloma virus | |
| | Varicella zoster virus | |
| **Non-Hodgkin's lymphoma** | | |

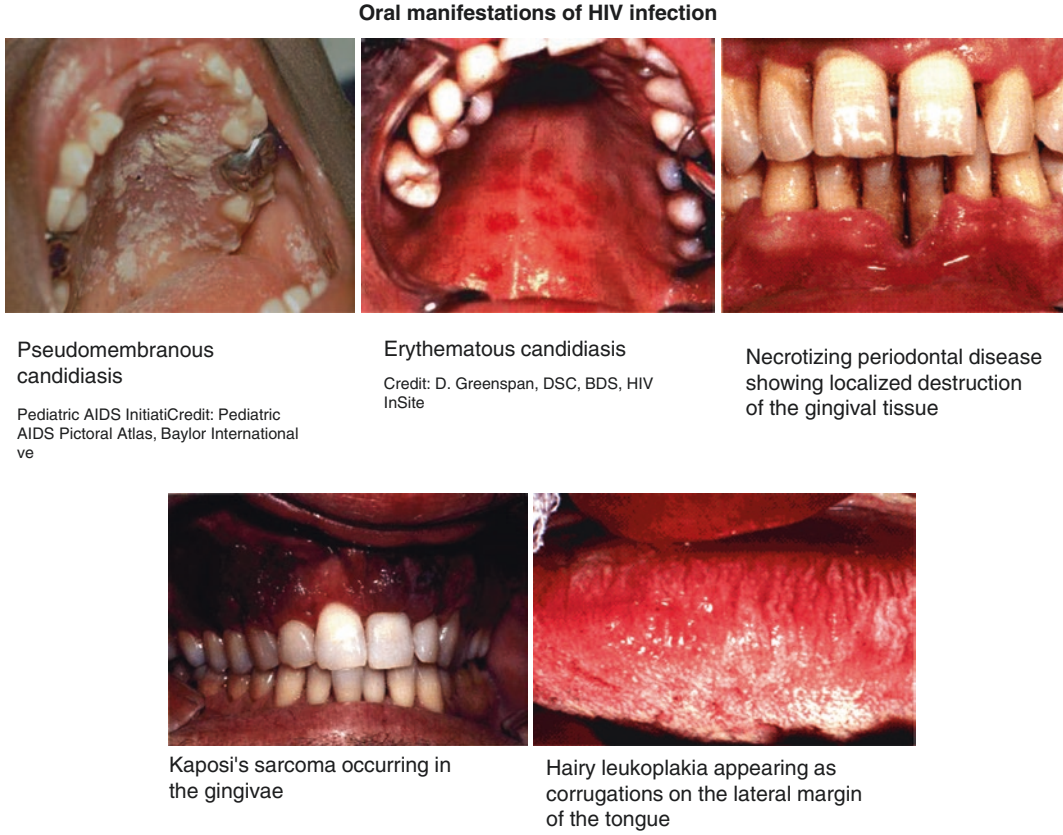


**Fig. 10.2** Oral manifestations of HIV

increases with time following seroconversion and is an indication that the patient is progressing from the asymptomatic phase to AIDS [96, 97].

While the oral cavity succumbs to infections and disease induced by the dysregulated immune system in HIV infection, the HIV virus is rarely found in the oral tissues and no productive infection is seen in oral epithelial cells [98–101].

### 10.1.4 Fungal Infections

*Candidiasis* can present both in the oral cavity and elsewhere, such as the vagina. The causative organism, *Candida albicans,* is a normal component of the oral flora in about 40% of the population. Clinical infection is influenced by the immune status of the individual as well as the strain of *Candida sp*. that is present and the overall composition of the individuals' oral flora.

The three clinical forms of candidiasis that occur most frequently are pseudo-membranous (thrush), erythematous and hyperplastic. There are also several variations within each group [102, 103]. The observations that oral candidiasis is frequent in HIV (Fig. 10.2) and in other immunodeficiency states, where T cell immunity is absent or compromised, strongly suggest a role for cellular immunity in preventing overt infection or transition from the commensal yeast to pathogenic hyphal forms [103, 104].

Many of the factors which predispose towards Candida infection can be directly linked to immune dysregulation, for example, extremes of age (both young and old) where the immune system is either not fully developed or is waning. Smoking is also known to change the types and functions of antigen-presenting cells (especially dendritic cells) in the oral mucosa and affects susceptibility to infection [105–107]. Pseudomembranous candidiasis

has also been associated with the use of asthma inhalers—which contain immune-modulatory pharmaceuticals [108].

IgA-deficient individuals are also highly susceptible to candidiasis suggesting a role for secretory IgA [109, 110].

Neutrophils are a key component in protection against candidiasis and IL-17 seems to be important in recruiting these cells into the oral epithelium [111, 112]. More recently the IL-17 receptor (IL-17R) signalling pathways in oral epithelial cells have been shown to be crucial in protection against candidiasis in a mouse model, through the production of the antimicrobial peptide, β-defensin 3 [113].

IL-17 has multiple roles in both immune protection and immunopathology. There is a well-recognised role in surveillance at mucosal and barrier surfaces [114]. However, IL-17 has also been implicated in driving autoimmunity and chronic inflammation [115, 116].

The sources of IL-17 are somewhat controversial as several different cell types can produce this cytokine including NKT, γδ T cells, macrophages and the relatively newly described *innate lymphoid* cells as well as Th17 helper cells [72, 117–119].

### Conclusion

The most common oral mucosal infections are caused by bacteria, viruses and fungi. Some Helminth and protozoal organisms also have the potential to produce oral manifestations of disease but are much rarer and have not been explored. The immune system contributes to both protection from infection and resolution of the inflammation induced by infection but also the immunopathological consequences of dysregulation and dysbiosis. The importance of immune mechanisms will be explored in the next chapter where noninfectious oral mucosal disease will be explored.

## References


1. Fedele S, Sabbah W, Donos N, Porter S, D'aiuto F. Common oral mucosal diseases, systemic inflammation, and cardiovascular diseases in a large cross-sectional US survey. Am Heart J. 2011;161:344–50.
2. Williams DM. Reducing inequalities in oral disease. Br Dent J. 2011;210:393. England.
3. Williams DM, Sheiham A, Honkala E. Addressing oral health inequalities in the Africa and middle east region. J Dent Res. 2015;94(7):875.
4. Needleman I, Ashley P, Petrie A, Fortune F, Turner W, Jones J, Niggli J, Engebretsen L, Budgett R, Donos N, Clough T, Porter S. Oral health and impact on performance of athletes participating in the London 2012 olympic games: a cross-sectional study. Br J Sports Med. 2013;47:1054–8.
5. Chapple ILC, Genco R, Workshop WGOTJEA. Diabetes and periodontal diseases: consensus report of the joint efp/aap workshop on periodontitis and systemic diseases. J Periodontol. 2013;84:S106–12.
6. Genco RJ, Van Dyke TE. Prevention: reducing the risk of CVD in patients with periodontitis. Nat Rev Cardiol. 2010;7:479–80.
7. Han YW, Wang X. Mobile microbiome: oral bacteria in extra-oral infections and inflammation. J Dent Res. 2013;92:485–91.
8. Kebschull M, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"—epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res. 2010;89:879–902.
9. Kholy KE, Genco RJ, Van Dyke TE. Oral infections and cardiovascular disease. Trends Endocrinol Metab. 2015;26:315–21.
10. Lundberg K, Wegner N, Yucel-Lindberg T, Venables PJ. Periodontitis in RA—the citrullinated enolase connection. Nat Rev Rheumatol. 2010;6:727–30.
11. Madianos PN, Bobetsis YA, Offenbacher S. Adverse pregnancy outcomes (APOs) and periodontal disease: pathogenic mechanisms. J Clin Periodontol. 2013;40(Suppl 14):S170–80.
12. Whitmore SE, Lamont RJ. Oral bacteria and cancer. PLoS Pathog. 2014;10:E1003933.
13. Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA. Increase in head and neck cancer in younger patients due to human papillomavirus (HPV). Oral Oncol. 2015;51:727–30.
14. Bergquist R. Parasitic infections affecting the oral cavity. Periodontol 2000. 2009;49:96–105.
15. Marcenes W, Kassebaum NJ, Bernabé E, Flaxman A, Naghavi M, Lopez A, Murray CJ. Global burden of oral conditions in 1990–2010: a systematic analysis. J Dent Res. 2013;92(7):592.
16. Topic B, Rascic-Konjhodzic H, Cizek Sajko M. Periodontal disease and dental caries from krapina neanderthal to contemporary man—skeletal studies. Acta Med Acad. 2012;41:119–30.
17. Weyrich LS, Dobney K, Cooper A. Ancient DNA analysis of dental calculus. J Hum Evol. 2015;79:119–24.
18. Weyrich LS, Duchene S, Soubrier J, Arriola L, Llamas B, Breen J, Morris AG, Alt KW, Caramelli D, Dresely V, Farrell M, Farrer AG, Francken M, Gully N, Haak W, Hardy K, Harvati K, Held P, Holmes EC, Kaidonis J, Lalueza-Fox C, De La Rasilla M, Rosas A, Semal P, Soltysiak A, Townsend G, Usai D, Wahl J, Huson DH, Dobney K, Cooper

A. Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. Nature. 2017. Advance Online Publication.
19. Russell MW, Lehner T. Characterisation of antigens extracted from cells and culture fluids of streptococcus mutans serotype C. Arch Oral Biol. 1978;23:7–15.
20. Lehner T, Russell MW, Caldwell J, Smith R. Immunization with purified protein antigens from streptococcus mutans against dental caries in rhesus monkeys. Infect Immun. 1981;34:407–15.
21. Lehner T, Russell MW, Wilton JM, Challacombe SJ, Scully CM, Hawkes JE. Passive immunization with antisera to streptococcus mutans in the prevention of caries in rhesus monkeys. Adv Exp Med Biol. 1978;107:303–15.
22. Challacombe SJ, Russell MW, Hawkes J. Passage of intact igg from plasma to the oral cavity via crevicular fluid. Clin Exp Immunol. 1978;34:417–22.
23. Challacombe SJ, Russell MW, Hawkes JE, Bergmeier LA, Lehner T. Passage of immunoglobulins from plasma to the oral cavity in rhesus monkeys. Immunology. 1978;35:923–31.
24. Lehner T, Russell MW, Challacombe SJ, Scully CM, Hawkes JE. Passive immunisation with serum and immunoglobulins against dental caries in rhesus monkeys. Lancet. 1978;1:693–5.
25. Challacombe SJ, Bergmeier LA, Czerkinsky C, Rees AS. Natural antibodies in man to streptococcus mutans: specificity and quantification. Immunology. 1984;52:143–50.
26. Challacombe SJ, Bergmeier LA, Rees AS. Natural antibodies in man to a protein antigen from the bacterium streptococcus mutans related to dental caries experience. Arch Oral Biol. 1984;29:179–84.
27. Kirtaniya BC, Chawla HS, Tiwari A, Ganguly NK, Sachdev V. Natural prevalence of antibody titers to glucosyltransferase of streptococcus mutans in serum in high and low caries active children. J Indian Soc Pedod Prev Dent. 2010;28:91–4.
28. Ma JK, Hunjan M, Smith R, Lehner T. Specificity of monoclonal antibodies in local passive immunization against streptococcus mutans. Clin Exp Immunol. 1989;77:331–7.
29. Ma JK, Smith R, Lehner T. Use of monoclonal antibodies in local passive immunization to prevent colonization of human teeth by streptococcus mutans. Infect Immun. 1987;55:1274–8.
30. Smith R, Lehner T, Beverley PC. Characterization of monoclonal antibodies to streptococcus mutans antigenic determinants I/Ii, I, Ii, and Iii and their serotype specificities. Infect Immun. 1984;46:168–75.
31. Ma JK, Hiatt A, Hein M, Vine ND, Wang F, Stabila P, Van Dolleweerd C, Mostov K, Lehner T. Generation and assembly of secretory antibodies in plants. Science. 1995;268:716–9.
32. Ma JK, Hikmat BY, Wycoff K, Vine ND, Chargelegue D, Yu L, Hein MB, Lehner T. Characterization of a recombinant plant monoclonal secretory antibody and preventive immunotherapy in humans. Nat Med. 1998;4:601–6.
33. Ma JK, Lehner T. Prevention of colonization of streptococcus mutans by topical application of monoclonal antibodies in human subjects. Arch Oral Biol. 1990;35(Suppl):115s–22s.
34. Smith DJ, Taubman MA. Oral immunization of humans with streptococcus sobrinus glucosyltransferase. Infect Immun. 1987;55:2562–9.
35. Yan YH, Yu F, Zeng C, Cao LH, Zhang Z, Xu QA. Ccl17 combined with Ccl19 as a nasal adjuvant enhances the immunogenicity of an anti-caries DNA vaccine in rodents. Acta Pharmacol Sin. 2016;37:1229–36.
36. Ferreira EL, Batista MT, Cavalcante RC, Pegos VR, Passos HM, Silva DA, Balan A, Ferreira LC, Ferreira RC. Sublingual immunization with the phosphate-binding-protein (Psts) reduces oral colonization by streptococcus mutans. Mol Oral Microbiol. 2016;31:410–22.
37. Hajishengallis G, Liang S, Payne MA, Hashim A, Jotwani R, Eskan MA, Mcintosh ML, Alsam A, Kirkwood KL, Lambris JD, Darveau RP, Curtis MA. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. Cell Host Microbe. 2011;10:497–506.
38. Lamont RJ, Hajishengallis G. Polymicrobial synergy and dysbiosis in inflammatory disease. Trends Mol Med. 2015;21:172–83.
39. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol. 2014;16:1024–33.
40. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol. 2012;10:717–25.
41. Curtis MA, Zenobia C, Darveau RP. The relationship of the oral microbiotia to periodontal health and disease. Cell Host Microbe. 2011;10:302–6.
42. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15:30–44.
43. Stabholz A, Soskolne WA, Shapira L. Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. Periodontol 2000. 2010;53:138–53.
44. Laine ML, Crielaard W. Functional foods/ingredients and periodontal diseases. Eur J Nutr. 2012;51(Suppl 2):S27–30.
45. Laine ML, Moustakis V, Koumakis L, Potamias G, Loos BG. Modeling susceptibility to periodontitis. J Dent Res. 2013;92:45–50.
46. Nussbaum G, Shapira L. How has neutrophil research improved our understanding of periodontal pathogenesis? J Clin Periodontol. 2011;38(Suppl 11):49–59.
47. Sima C, Glogauer M. Neutrophil dysfunction and host susceptibility to periodontal inflammation: current state of knowledge. Current Oral Health Reports. 2014;1:95–103.
48. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol. 2010;8:481–90.
49. Hajishengallis E, Hajishengallis G. Neutrophil homeostasis and periodontal health in children and adults. J Dent Res. 2014;93:231–7.

50. Moutsopoulos NM, Konkel J, Sarmadi M, Eskan MA, Wild T, Dutzan N, Abusleme L, Zenobia C, Hosur KB, Abe T, Uzel G, Chen W, Chavakis T, Holland SM, Hajishengallis G. Defective neutrophil recruitment in leukocyte adhesion deficiency type I disease causes local Il-17-driven inflammatory bone loss. Sci Transl Med. 2014;6:229ra40.
51. Chapple IL, Matthews JB. The role of reactive oxygen and antioxidant species in periodontal tissue destruction. Periodontol 2000. 2007;43:160–232.
52. Eskan MA, Jotwani R, Abe T, Chmelar J, Lim JH, Liang S, Ciero PA, Krauss JL, Li F, Rauner M, Hofbauer LC, Choi EY, Chung KJ, Hashim A, Curtis MA, Chavakis T, Hajishengallis G. The leukocyte integrin antagonist Del-1 inhibits Il-17-mediated inflammatory bone loss. Nat Immunol. 2012;13:465–73.
53. Ryder MI. Comparison of neutrophil functions in aggressive and chronic periodontitis. Periodontol 2000. 2010;53:124–37.
54. Teles RP, Gursky LC, Faveri M, Rosa EA, Teles FR, Feres M, Socransky SS, Haffajee AD. Relationships between subgingival microbiota and GCF biomarkers in generalized aggressive periodontitis. J Clin Periodontol. 2010;37:313–23.
55. De Lima Oliveira AP, De Faveri M, Gursky LC, Mestnik MJ, Feres M, Haffajee AD, Socransky SS, Teles RP. Effects of periodontal therapy on GCF cytokines in generalized aggressive periodontitis subjects. J Clin Periodontol. 2012;39:295–302.
56. Sasaki H, Okamatsu Y, Kawai T, Kent R, Taubman M, Stashenko P. The interleukin-10 knockout mouse is highly susceptible to porphyromonas gingivalis-induced alveolar bone loss. J Periodontal Res. 2004;39:432–41.
57. Sasaki H, Suzuki N, Kent R, Kawashima N, Takeda J, Stashenko P. T cell response mediated by myeloid cell-derived Il-12 is responsible for porphyromonas gingivalis-induced periodontitis in Il-10-deficient mice. J Immunol. 2008;180:6193–8.
58. Jusko M, Potempa J, Karim AY, Ksiazek M, Riesbeck K, Garred P, Eick S, Blom AM. A metalloproteinase karilysin present in the majority of tannerella forsythia isolates inhibits all pathways of the complement system. J Immunol. 2012;188:2338–49.
59. Malm S, Jusko M, Eick S, Potempa J, Riesbeck K, Blom AM. Acquisition of complement inhibitor serine protease factor I and its cofactors C4b-binding protein and factor H by prevotella intermedia. PLoS One. 2012;7:E34852.
60. Popadiak K, Potempa J, Riesbeck K, Blom AM. Biphasic effect of gingipains from porphyromonas gingivalis on the human complement system. J Immunol. 2007;178:7242–50.
61. Shin JE, Baek KJ, Choi YS, Choi Y. A periodontal pathogen treponema denticola hijacks the fusobacterium nucleatum-driven host response. Immunol Cell Biol. 2013;91:503–10.
62. Booth V, Ashley FP, Lehner T. Passive immunization with monoclonal antibodies against porphyromonas gingivalis in patients with periodontitis. Infect Immun. 1996;64:422–7.
63. Booth V, Lehner T. Characterization of the porphyromonas gingivalis antigen recognized by a monoclonal antibody which prevents colonization by the organism. J Periodontal Res. 1997;32:54–60.
64. Kelly CG, Booth V, Kendal H, Slaney JM, Curtis MA, Lehner T. The relationship between colonization and haemagglutination inhibiting and B cell epitopes of porphyromonas gingivalis. Clin Exp Immunol. 1997;110:285–91.
65. O'brien-Simpson NM, Holden JA, Lenzo JC, Tan Y, Brammar GC, Walsh KA, Singleton W, Orth RKH, Slakeski N, Cross KJ, Darby IB, Becher D, Rowe T, Morelli AB, Hammet A, Nash A, Brown A, Ma B, Vingadassalom D, Mccluskey J, Kleanthous H, Reynolds EC. A therapeutic porphyromonas gingivalis gingipain vaccine induces neutralising Igg1 antibodies that protect against experimental periodontitis. npj Vaccines. 2016;1:16022.
66. Hasan A, Sadoh D, Palmer R, Foo M, Marber M, Lehner T. The immune responses to human and microbial heat shock proteins in periodontal disease with and without coronary heart disease. Clin Exp Immunol. 2005;142:585–94.
67. Ebersole JL. Humoral immune responses in gingival crevice fluid: local and systemic implications. Periodontol 2000. 2003;31:135–66.
68. Kinane DF, Mooney J, Ebersole JL. Humoral immune response to actinobacillus actinomycetemcomitans and porphyromonas gingivalis in periodontal disease. Periodontol 2000. 1999;20:289–340.
69. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Aust Dent J. 2009;54(Suppl 1):S2–10.
70. Cheng W-C, Hughes FJ, Taams LS. The presence, function and regulation of Il-17 and Th17 cells in periodontitis. J Clin Periodontol. 2014;41:541–9.
71. Cheng WC, Van Asten SD, Burns LA, Evans HG, Walter GJ, Hashim A, Hughes FJ, Taams LS. Periodontitis-associated pathogens *P. gingivalis* and *A. actinomycetemcomitans* activate human Cd14(+) monocytes leading to enhanced Th17/Il-17 responses. Eur J Immunol. 2016;46:2211–21.
72. Abusleme L, Moutsopoulos NM. Il-17: overview and role in oral immunity and microbiome. Oral Dis. 2016;23:854–65.
73. Hajishengallis G, Moutsopoulos NM. Role of bacteria in leukocyte adhesion deficiency-associated periodontitis. Microb Pathog. 2016;94:21–6.
74. Kinane D, Bouchard P. Periodontal diseases and health: consensus report of the sixth european workshop on periodontology. J Clin Periodontol. 2008;35:333–7.
75. Persson GR, Persson RE. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol. 2008;35:362–79.

76. Sahingur SE, Yeudall WA. Chemokine function in periodontal disease and oral cavity cancer. Front Immunol. 2015;6:214.
77. Ebersole JL, Kirakodu SS, Novak MJ, Orraca L, Martinez JG, Cunningham LL, Thomas MV, Stromberg A, Pandruvada SN, Gonzalez OA. Transcriptome analysis of B cell immune functions in periodontitis: mucosal tissue responses to the oral microbiome in aging. Front Immunol. 2016;7:272.
78. Ebersole JL, Dawson DR 3rd, Morford LA, Peyyala R, Miller CS, Gonzalez OA. Periodontal disease immunology: 'double indemnity' in protecting the host. Periodontol 2000. 2013;62:163–202.
79. Soames J, Southam J. Oral pathology. Oxford, UK: Oxford University Press; 2008.
80. Koelle DM, Corey L. Recent progress in herpes simplex virus immunobiology and vaccine research. Clin Microbiol Rev. 2003;16:96–113.
81. Kim DY, Cho S, Choi MJ, Sohn S, Lee ES, Bang D. Immunopathogenic role of herpes simplex virus in Behcet's disease. Genet Res Int. 2013;638273:24.
82. Hatemi G, Yazici H. Behçet's syndrome and micro-organisms. Best Pract Res Clin Rheumatol. 2011;25:389–406.
83. Young C, Lehner T, Barnes CG. Cd4 and Cd8 cell responses to herpes simplex virus in Behçet's disease. Clin Exp Immunol. 1988;73:6–10.
84. Khanna KM, Bonneau RH, Kinchington PR, Hendricks RL. Herpes simplex virus-specific memory Cd8+ T cells are selectively activated and retained in latently infected sensory ganglia. Immunity. 2003;18:593–603.
85. Pollara G, Katz DR, Chain BM. The host response to herpes simplex virus infection. Curr Opin Infect Dis. 2004;17:199–203.
86. Slots J, Saygun I, Sabeti M, Kubar A. Epstein-Barr virus in oral diseases. J Periodontal Res. 2006;41:235–44.
87. Seoudi N, Bergmeier LA, Hagi-Pavli E, Bibby D, Fortune F. The seroprevalence and salivary shedding of herpesviruses in Behçet's syndrome and recurrent aphthous stomatitis. J Oral Microbiol. 2015;7:27156.
88. Seoudi N, Bergmeier LA, Drobniewski F, Paster B, Fortune F. The oral mucosal and salivary microbial community of Behcet's syndrome and recurrent aphthous stomatitis. J Oral Microbiol. 2015;7:27150.
89. Seoudi N, Bergmeier LA, Hagi-Pavli E, Bibby D, Curtis MA, Fortune F. The role of Tlr2 and 4 in Behcet's disease pathogenesis. Innate Immun. 2014;20:412–22.
90. Rohner E, Wyss N, Heg Z, Faralli Z, Mbulaiteye SM, Novak U, Zwahlen M, Egger M, Bohlius J. HIV and human herpesvirus 8 co-infection across the globe: systematic review and meta-analysis. Int J Cancer. 2016;138:45–54.
91. Rohner E, Wyss N, Trelle S, Mbulaiteye SM, Egger M, Novak U, Zwahlen M, Bohlius J. Hhv-8 seroprevalence: a global view. Syst Rev. 2014;3:11.
92. Huhns M, Simm G, Erbersdobler A, Zimpfer A. HPV infection, but not EBV or HHV-8 infection, is associated with salivary gland tumours. Biomed Res Int. 2015;2015:829349.
93. Rautava J, Syrjanen S. Human papillomavirus infections in the oral mucosa. J Am Dent Assoc. 2011;142:905–14.
94. Syrjanen S, Lodi G, Von Bultzingslowen I, Aliko A, Arduino P, Campisi G, Challacombe S, Ficarra G, Flaitz C, Zhou HM, Maeda H, Miller C, Jontell M. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Dis. 2011;17(Suppl 1):58–72.
95. Cleveland JL, Junger ML, Saraiya M, Markowitz LE, Dunne EF, Epstein JB. The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. J Am Dent Assoc. 2011;142:915–24.
96. Greenspan JS. Sentinels and signposts: the epidemiology and significance of the oral manifestations of HIV disease. Oral Dis. 1997;3(Suppl 1):S13–7.
97. Lifson AR, Hilton JF, Westenhouse JL, Canchola AJ, Samuel MC, Katz MH, Buchbinder SP, Hessol NA, Osmond DH, Shiboski S, Et A. Time from HIV seroconversion to oral candidiasis or hairy leukoplakia among homosexual and bisexual men enrolled in three prospective cohorts. AIDS. 1994;8:73–9.
98. Challacombe SJ, Naglik JR. The effects of HIV infection on oral mucosal immunity. Adv Dent Res. 2006;19:29–35.
99. Kohli A, Islam A, Moyes DL, Murciano C, Shen C, Challacombe SJ, Naglik JR. Oral and vaginal epithelial cell lines bind and transfer cell-free infectious HIV-1 to permissive cells but are not productively infected. PLoS One. 2014;9:E98077.
100. Moyes DL, Islam A, Kohli A, Naglik JR. Oral epithelial cells and their interactions with HIV-1. Oral Dis. 2016;22(Suppl 1):66–72.
101. Wood LF, Chahroudi A, Chen H-L, Jaspan HB, Sodora DL. The oral mucosa immune environment and oral transmission of HIV/SIV. Immunol Rev. 2013;254:34–53.
102. Moyes DL, Wilson D, Richardson JP, Mogavero S, Tang SX, Wernecke J, Hofs S, Gratacap RL, Robbins J, Runglall M, Murciano C, Blagojevic M, Thavaraj S, Forster TM, Hebecker B, Kasper L, Vizcay G, Iancu SI, Kichik N, Hader A, Kurzai O, Luo T, Kruger T, Kniemeyer O, Cota E, Bader O, Wheeler RT, Gutsmann T, Hube B, Naglik JR. Candidalysin is a fungal peptide toxin critical for mucosal infection. Nature. 2016;532:64–8.
103. Naglik JR, Richardson JP, Moyes DL. Candida albicans pathogenicity and epithelial immunity. PLoS Pathog. 2014;10:E1004257.
104. Moyes DL, Naglik JR. Mucosal immunity and candida albicans infection. Clin Dev Immunol. 2011;2011:346307.
105. Boyle JO, Gümüs ZH, Kacker A, Choksi VL, Bocker JM, Zhou XK, Yantiss RK, Hughes DB,

Du B, Judson BL, Subbaramaiah K, Dannenberg AJ. Effects of cigarette smoke on the human oral mucosal transcriptome. Cancer Prev Res (Phila). 2010;3:266–78.
106. Cruchley AT, Williams DM, Farthing PM, Speight PM, Lesch CA, Squier CA. Langerhans cell density in normal human oral mucosa and skin: relationship to age, smoking and alcohol consumption. J Oral Pathol Med. 1994;23:55–9.
107. Hovav AH. Dendritic cells of the oral mucosa. Mucosal Immunol. 2014;7:27–37.
108. Thomas MS, Parolia A, Kundabala M, Vikram M. Asthma and oral health: a review. Aust Dent J. 2010;55:128–33.
109. Lehner T, Challacombe SJ, Ivanyi L, Wilton JM. The relationship between serum and salivary antibodies and cell-mediated immunity in oral disease in man. Adv Exp Med Biol. 1974;45:485–95.
110. Lehner T, Wilton JM, Ivanyi L. Immunodeficiencies in chronic muco-cutaneous candidosis. Immunology. 1972;22:775–87.
111. Conti HR, Peterson AC, Brane L, Huppler AR, Hernández-Santos N, Whibley N, Garg AV, Simpson-Abelson MR, Gibson GA, Mamo AJ, Osborne LC, Bishu S, Ghilardi N, Siebenlist U, Watkins SC, Artis D, Mcgeachy MJ, Gaffen SL. Oral-resident natural Th17 cells and Γδ T cells control opportunistic candida albicans infections. J Exp Med. 2014;211:2075–84.
112. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, Ho AW, Hai JH, Yu JJ, Jung JW, Filler SG, Masso-Welch P, Edgerton M, Gaffen SL. Th17 Cells and Il-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med. 2009;206:299–311.
113. Conti HR, Bruno VM, Childs EE, Daugherty S, Hunter JP, Mengesha BG, Saevig DL, Hendricks MR, Coleman BM, Brane L, Solis N, Cruz JA, Verma AH, Garg AV, Hise AG, Richardson JP, Naglik JR, Filler SG, Kolls JK, Sinha S, Gaffen SL. Il-17 receptor signaling in oral epithelial cells is critical for protection against oropharyngeal candidiasis. Cell Host Microbe. 2016;20:606–17.
114. Song X, He X, Li X, Qian Y. The roles and functional mechanisms of interleukin-17 family cytokines in mucosal immunity. Cell Mol Immunol. 2016;13:418–31.
115. Gaffen SL, Herzberg MC, Taubman MA, Van Dyke TE. Recent advances in host defense mechanisms/therapies against oral infectious diseases and consequences for systemic disease. Adv Dent Res. 2014;26:30–7.
116. Gaffen SL, Jain R, Garg AV, Cua DJ. The Il-23-Il-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol. 2014;14:585–600.
117. Cua DJ, Tato CM. Innate Il-17-producing cells: the sentinels of the immune system. Nat Rev Immunol. 2010;10:479–89.
118. Hernandez-Santos N, Gaffen SL. Th17 cells in immunity to candida albicans. Cell Host Microbe. 2012;11:425–35.
119. Hernandez-Santos N, Huppler AR, Peterson AC, Khader SA, Mckenna KC, Gaffen SL. Th17 cells confer long-term adaptive immunity to oral mucosal candida albicans infections. Mucosal Immunol. 2013;6:900–10.