Nano TransMed 2 (2023) 100001

Contents lists available at ScienceDirect

Nano TransMed

journal homepage: www.keaipublishing.com/en/journals/nano-transmed/

# Immune-mediated conditions and cellular biomarkers for early diagnosis of oral diseases

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ARTICLE INFO

*Keywords:*
Oral immunology
Immune mediated oral diseases
Hypersensitivity
Immunodeficiency disorders
Cellular biomarkers
Cytokines

ABSTRACT

Oral signs and symptoms are frequently the first manifestation of immunological conditions. The dentists can therefore play an important role in the detection and during the management phase of the multidisciplinary treatment. Precise and early diagnosis increases the efficiency and efficacy of treatment strategy. This review provided an update of the immune system, the common immunological conditions that show oral clinical signs and symptoms, and guidance as to the appropriate investigation needed to differentiate and correctly diagnoses these conditions.

## 1. Introduction

Microorganisms represent a constant threat to our body. Most multicellular organisms have evolved some types of immune response to microorganisms that threaten their lives. In fact, humans have a complex and effective immune system that recognises and removes harmful substances, protects the body from pathogens such as viruses, bacteria and parasites that cause the diseases. The mechanisms of immunity are evolutionarily selected throughout host-pathogen interaction to differentiate between the individual's own cells and those of harmful organisms while not attacking the beneficial commensal flora.

Oral mucosa is physically connected between skin and gastrointestinal mucosa and possesses characteristics of both. The main structural features of the oral mucosa are the oral epithelium, lamina propria and submucosa. The oral mucosa consists of stratified squamous epithelium and contains several layers of cells with different morphologies. Other cell types such as melanocytes, Langerhans cells, Merkel cells, and immunocytes make up to 10 % of the cell population in the oral epithelium besides keratinocytes [1]. Keratinocytes and Langerhans cells play an important role in the immunosurveillance of the oral epithelium, and both can secrete and respond to cytokines, such as interleukins and interferons, which can activate T cells so that they are capable of responding to antigenic challenge. Apart from Langerhans cells, a number of immunocytes often are seen in the nucleated cell layers. Lymphocytes are the most common cell type, while polymorphonuclear neutrophils and mast cells are uncommon.

The oral cavity is composed of sophisticated anatomical structures, and it is home to one of the most complex microbial ecosystems. The oral cavity, which is part of the mucosal immune system, is constantly bathed in a potentially dangerous, harmful and rapidly changing environment. The innate (non-specific) and adaptive (specific) immune responses work together against harmful germs and substances. The oral mucosa serves several functions. In addition to protecting the deeper tissues of the oral cavity, oral mucosa serves as a sensory organ, site of secretion, and regulator of temperature. Various mucosa-associated lymphoid tissues regulate immune responses in the buccal mucosa. They are part of Waldeyer's ring, which consists of the pharyngeal tonsil, the tubal tonsils, the palatine tonsils, and the lingual tonsils [2]. The oral mucosa is constantly bathed in saliva. Saliva has a major ecologic influence on the pathogens that colonise oral tissues. It has many functions, such as protection, buffering, pellicle formation, maintenance of tooth integrity, antimicrobial action, tissue repair, digestion and taste, the most important being protection of the oral cavity. It not only

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Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.ntm.2023.100001
Received 14 March 2023; Received in revised form 10 July 2023; Accepted 16 July 2023
Available online 5 October 2023

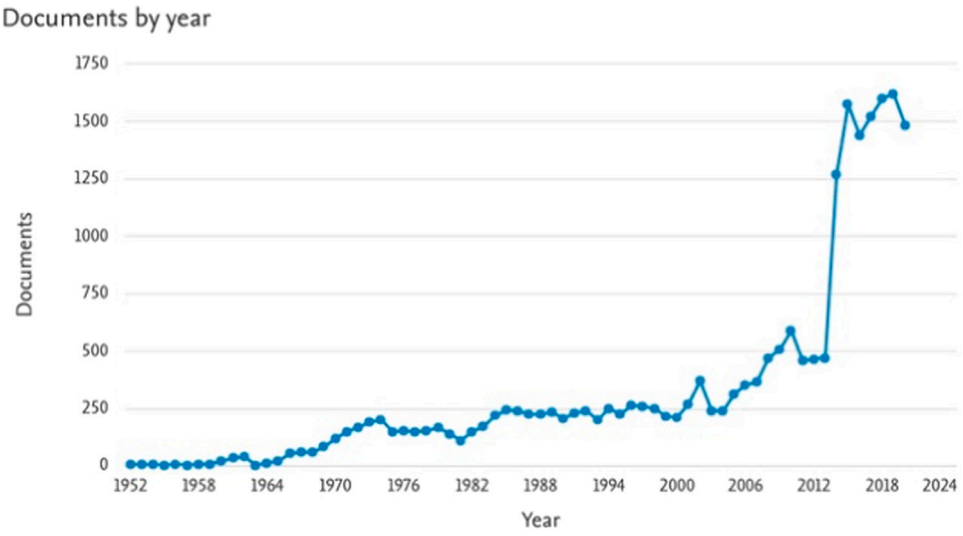


**Fig. 1.** There was an increased trend for the research of oral immunology since 2003. A significant increase was noted in 2012 (Based on the Scopus database).

provides a washing action that flushes away nonadherent bacteria and other debris, but also contains a variety of antimicrobial properties of defensins, histatins, cystatin, peroxidase, lysozyme, lactoferrin, IgG, IgM and secretory IgA [3].

However, the immune system can sometimes fail in one of the three ways and resulting in hypersensitivity (overactivity of the response to an antigen), immunodeficiency (underactivity of the response to a pathogen) and autoimmunity (reaction against own tissues). This review provided an overview of literature in the last two decades of the immune system, hypersensitivity, and immunodeficiency disorders. "Oral immunology" within "Article title, Abstract, Keywords" in the Scopus database were searched. It has shown an increased trend for the research of oral immunology since 2003. It was noted that there was a significant increase in publication in 2012 (Fig. 1). Most of the articles were published in Frontiers in immunology, Plos One, Annals of allergy asthma and immunology, Journal of allergy and clinical immunology, and Vaccine (Fig. 2). United States, Japan, China, United Kingdom and Germany were the top five countries that conducted most of the oral immunology (Fig. 3). Most of the subjects are related to medicine, immunology and biochemistry (Fig. 4).

## 2. Clinical immunology

### 2.1. Cells of the immune system

The immune system is made up of special organs, tissues, cells, proteins and molecules that fight infections. Although the leukocytes are the central to all immune responses, other cells and tissues also participate by signalling to the lymphocytes and responding to cytokines released by T cells and monocytes.

### 2.2. Phagocytes

The mononuclear phagocyte lineage constitutes important long-lived phagocytic cells spread throughout the human body. They are derived from bone marrow, and able to engulf and internalise pathogens [4]. To do so, they have different surface receptors or antibodies that allow them to recognise and bind to a wide range of pathogens [5]. Phagocytosis is a process that describes the internalisation of particles or microorganism. The primordial reactions of phagocytes are very efficient, and patients with deficiencies in phagocytic function often

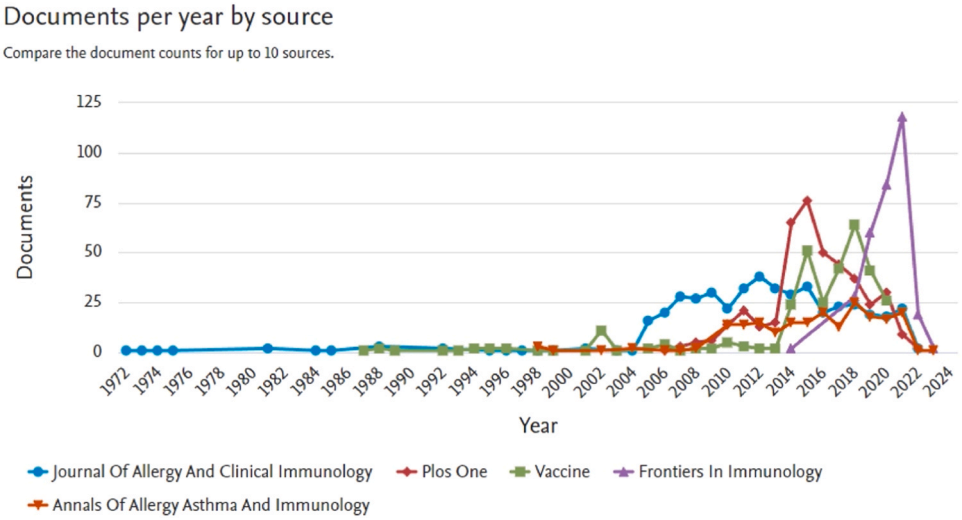


**Fig. 2.** Most of the articles were published in Frontiers in immunology, Plos One, Annals of allergy asthma and immunology, Journal of allergy and clinical immunology, and Vaccine (Based on the Scopus database).

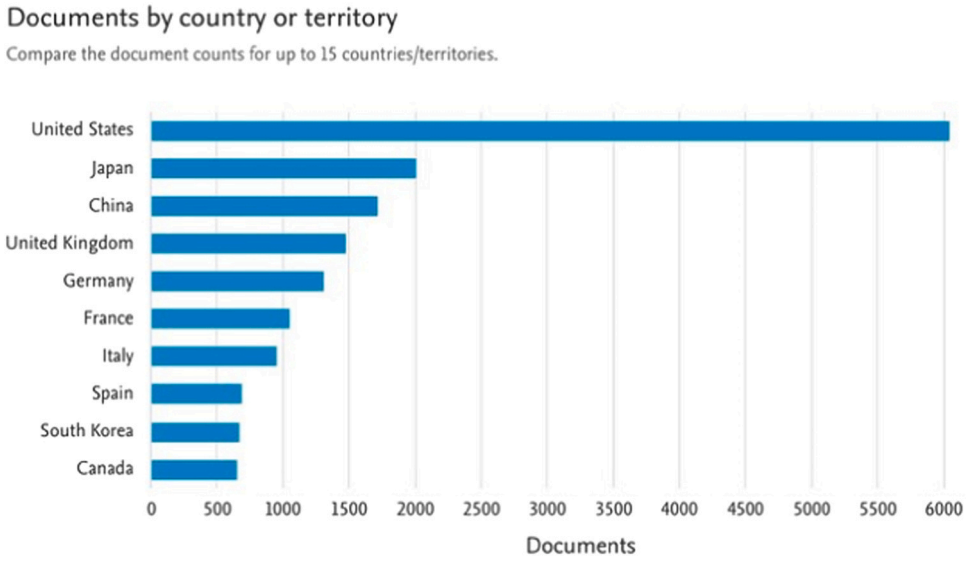


**Fig. 3.** United States, Japan, China, United Kingdom and Germany were the top five countries in oral immunology publication (Based on the Scopus database).

experience early infection propagation, resulting in severe sepsis and an increased risk of death [6]. Monocytes are the main type of mononuclear phagocyte lineage in the blood. They develop into macrophages when they migrate from the blood into tissues. Polymorphonuclear neutrophils are another important group of phagocytes. They are the main protagonists of the innate immune response that phagocytose pathogens and release cytotoxins, particularly at sites of inflammation [7]. However, they are short-lived and die upon spontaneous apoptosis. Extended lifespan has been observed among those cells arrive at the inflammation sites with microbial challenges [8].

### 2.3. Lymphocytes

Adaptive immune responses are mediated by a group of leukocytes called lymphocytes, which include T and B lymphocytes (T cells and B cells) that specialised in recognising antigens. Each lymphocyte entering the bloodstream bears antigen-specific membrane receptors. The specificity of these receptors is controlled by a unique genetic process that produces several variations of the receptor-encoding genes during lymphocyte development in the bone marrow and thymus [9]. There are three major types of lymphocytes, such as B cells (bone-marrow-derived cells), T cells (thymus cells) and ILCs (innate lymphoid cells).

B cells express specific antigen receptors (antibody/immunoglobulin; Ig) on their cell surface during their development. There are five main classes of immunoglobulin, namely IgA, IgD, IgE, IgG and IgM. They are different in size, charge, amino acid sequence and carbohydrate content [10]. Each immunoglobulin class has a distinct heavy chain type, such as α (IgA), δ (IgD), ε (IgE), γ (IgG) and μ (IgM). Alteration in the structure of the heavy chain within a class gives rise to subclasses of immunoglobulin. In human there are four subclasses of IgG (IgG1, IgG2, IgG3, and IgG4) and two IgA (IgA1 and IgA2). IgM and/or IgD is initially expressed in immature B cell, but once matured they may express IgA, IgE, IgG or retain IgM expression, and secrete them into the extracellular fluid [11]. Each B cell is programmed to express a unique surface receptor for a particular antigen. If the B cell binds to a specific antigen, it will multiply and differentiate into plasma

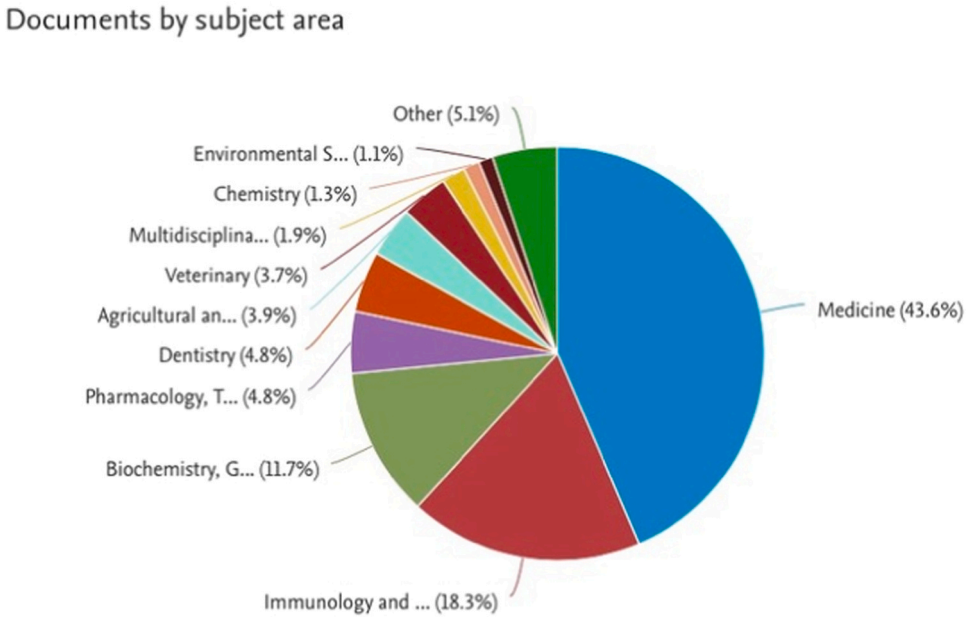


**Fig. 4.** Most of the subjects are related to medicine, immunology and biochemistry (Based on the Scopus database).

cells, which are capable of producing large amounts of antibody. Antibodies are essential components of the immune response, and they help the phagocytes to engulf the antigen via a process called opsonisation.

There are five major types of T cells, namely helper T cells (Th), cytotoxic T cell (Tc), natural killer T cells (NKT), gamma delta T cells (γδT) and mucosal-associated invariant T (MAIT) cells.

Helper T cells, known as $CD4^+$ T cells, are play a crucial role in adaptive immunity. In addition to assisting in the activation of B cells to release antibodies and macrophages to destroy ingested microorganisms, they also assist in the activation of cytotoxic T lymphocytes to kill infected target cells. Based on their cytokine production, expression of lineage-specifying transcription factors (TFs) and chemokine receptors and immune regulatory functions, Th cells can differentiate into several distinct subtypes, including Th1, Th2, Th9, Th17, Th22, T follicular helper (Tfh) or regulatory T cell (Treg)[12].

Th1 cells are a subset of T cells characterized by the expression of transcription factor T-box protein expressed in T cells (T-bet) and signal transducer and activator of transcription (STAT) 4 and the production of interleukin (IL)–2 and IFN-γ [13]. Th1 cells give rise to cell-mediate immunity and interacts with mononuclear phagocytes to destroy the intracellular pathogens. Th2 cells express the transcription factor GATA binding protein 3 (Gata-3) and STAT6 and secrete IL-4, IL-5, IL-10 and IL-13[13]. Th2 leads to a humoral immune response, and stimulates B cell to divide, differentiate and produce antibodies. Th9 cells, is a new subgroup of $CD4^+$ T cells, express the transcription PU.1 and IL-9, and play an important role in many immune-related diseases, such as tumours, inflammatory disease and parasite infection [14]. Th17 is a third major subset of helper T cells that can produce pro-inflammatory cytokine IL-17A, IL-17F, IL-21 and IL-22 [15]. Th17 cells express lineage-specific transcription factor retinoic acid-related orphan receptor gamma t (RORγt) [16]. Th17 cells play an important role in maintaining mucosal barrier, autoimmune disease and inflammatory disorder. Th22 cells, new player in the adaptive immunity are characterized by the expression of chemokine receptor CCR4, CCR6 and CCR10 [17]. Th22 cells can produce IL-22, IL-13, TNF-α but not IL-17, IL-4, or IFN-γ [18]. Th22 cells have been demonstrate to play a role in skin inflammatory diseases and involve the development of many autoimmune disorders.

Tfh cells, a specialized subset of CD4 + T cells, express high levels of programmed cell death-1 (PD-1), inducible T cell co-stimulator (ICOS) and the chemokine receptor CXCR5 and the lineage-defining transcription factor BCL6 [19]. Tfh cells collaborate with B cells to promote and regulate humoral responses.

Treg cells, a specialized subset T cells, can regulate or suppress immune response and maintain immune homeostasis and self-tolerance. They play a pivotal role in preventing the autoimmune diseases and limiting the chronic inflammatory diseases [20]. The differentiation of Treg cells depends on a key transcription factor forkhead box P3 (FOXP3). Treg cells supress other immune cells by the production of inhibitory cytokines, such as IL-10 and TGF-β [21].

Tc cells are responsible for the destruction of the infected host cells by programming them to undergo apoptosis [9]. The majority of Tc cells are $CD8^+$ T cells with MHC-restricted cytotoxicity and they have the ability to identify antigen in the presence of MHC class I antigens. Some Tc cells are $CD4^+$ T cells and MHC class II restricted [22].

NKT cells are a subset of T cells that express NK cell markers and a restricted T-cell receptors [23]. They can recognize lipids and glycolipids presented by CD1d molecules, a member of the CD1 family of antigen-presenting molecules, rather than common peptide-major histocompatibility complexes (MHCs). Activated NKT cells can produce large quantities of IFN-γ, IL-4, and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as some other cytokines such as IL-2, IL-10, IL-13, IL-17, IL-21, and TNF-α [24].

γδ T cells are an unconventional subset of T cells that have a distinctive T-cell receptor (TCR) γ and δ chains on their surface. Unlike conventional αβ T cells, γδ T cells are more abundant at the barriers, such as skin, gut, lung than in peripheral blood. γδ T cells can connect crux inflammation of the adaptive and innate immunity by production of various cytokines, such as GM-CSF, IL-4, IL-17, IL-21, IL-22, and IFN-γ [25].

MAIT cells are innate-like T cells that are distinguished by their semi-invariant αβ T cell receptor (TCR) that identifies small-molecule biosynthetic products of riboflavin production displayed on the restriction molecule major histocompatibility complex (MHC)-related protein-1 (MR1)[26].

ILCs mainly populate mucosal sites, such as the oral mucosa. ILCs maintain barrier integrity and protect against various pathogenic challenges while they promote allergic and autoimmune diseases when inappropriately stimulated. Based on the differences of their developmental and effector program by the expression of lineage-specifying transcription factors and signalling molecules, ILC cells are divided into three major groups.

Mature ILCs can be divided into cytotoxic and non-cytotoxic helper ILCs [27]. Natural killer cells (NK) cells are the cytotoxic killer ILCs. Non-cytotoxic helper ILCs are further classified into three major groups named ILC1s, ILC2s and ILC3s [28].

NK cells have the capacity to recognise the surface changes of several types of cancer cells and microbial infected cells by limiting their spread and subsequent tissue damage [29].

ILC1s express transcription factor T-bet or Eomes and promote type 1 immune response via the production of IFN-γ and TNF-α in response to IL-12, IL-15, and IL-18 [30]. ILC2s, the innate counterpart of Th2, express transcription factor GATA-3, and produce the cytokines IL-4, IL-5, IL- and IL-13, and amphiregulin in response to TSLP, IL-25, and IL-33 [30]. They play a role in antihelmintic immunity, immune surveillance, immune regulation and wound healing. ILC3s, the innate counterparts of Th17, express the transcription factor RORγt and produce IL-17 and IL-22 in response to IL-23 and IL-1β [31]. ILC3s can also produce IL-2, IL-26, GM-CSF and TNF-α and leukemia inhibitory factor (LIF).

### 2.4. Other cytotoxic cells

Cytotoxic cells include eosinophils [32,33]. Eosinophils are known to contribute to both innate and adaptive immune responses and they are able to defence against intracellular bacteria and extracellular parasites, such as schistosomes, and modulate immediate hypersensitivity reactions [34].

### 2.5. Auxiliary cells and cellular fragment

Inflammation is also mediated by a variety of other immunocytes and cellular fragments such as basophils, mast cells and platelets. Basophils (Mobile, circulating cells) and mast cells are functional similarities, and thought to be represent primary effector cells in IgE dependent host responses to parasites and allergies diseases, and may have other important functions in physiological and pathological responses. Platelet is a small cellular fragment, which is essential in blood clotting, but they can also mediate inflammation, express and use receptors to bind infectious pathogen or pathogen-IgG immune complexes via Fc receptors on the platelet [35].

### 2.6. Innate immunity

Our immune response can be broadly divided into innate immunity and adaptive responses. Innate immune responses are the first line of defence against infection; however, they are not specific to a particular pathogen in the way that the adaptive immune responses are. The cells and molecules of innate responses are rapidly activated by encounter microbial invasion or tissue injury. This rapid response is essential due to fast-growing bacteria. The components of the innate immunity comprise biological barriers (e.g. skin and mucous barriers), chemicals

(e.g. gastric acid), cells (e.g. dendritic cells, granulocytes, and natural killer cells) and humoral defence mechanisms (e.g. secreted antibodies, complement, and certain antimicrobial peptides) [29]. The epithelium of skin and mucosal tissue functions like a mechanical barrier to the pathogens. Several important antimicrobial peptides such as defensins, lysozyme and cathelicidin are expressed or produced by the epithelial cells [36]. In contrast to the adaptive immune system, which depends on B and T cells, innate immune response is performed by cells such as ILCs, dendritic cells, macrophages, neutrophils, basophils, mast cells, and eosinophils. An important function of innate immunity is the rapid recruitment of these cells to the sites of infection and inflammation via the production of cytokines and chemokines. Those important cytokines/chemokines, such as tumour necrosis factor (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6) that are released at the early stage of innate immune response [37]. They are critical for immunologic responses, inflammation, metabolism, and haematopoiesis. Dysregulation of cytokines and chemokines is often associated with inflammatory or autoimmune diseases.

The complement system is part of the innate immune system and plays a crucial role in the innate defence against common pathogens. It can be activated at the early stage of infection in the absence of antibodies. The functions of the complement system include [29]:

1. The activation of inflammation and recruitment of inflammatory cells,
2. Opsonisation of pathogens, and clearance of immune complexes and apoptotic cells,
3. Directive microbial killing by lysis and development of antibody responses.

The complement system has three primary activation mechanisms: classical, lectin, and alternative. The classical pathway links to the adaptive immune system and is activated by antibody bound to antigen. In the classical pathway, C1q recognises mostly charged patterns and binds to their target molecules, including IgM and IgG containing immune complexes. However, the alternative and lectin pathways provide antibody-independent innate immunity. The lectin pathway is activated by microbial carbohydrates and differs from the classical pathway in the initial recognition and activation stages. The alternative pathway is in a constant state of low-level activation [38]. Its activation is accelerated by interaction between microbial surface and C3b [39]. All three pathways involve the activation of C3 to C3b and comprise a proteolytic cascade in which complexes of complement proteins create enzymes that cleave other complement in an ordered manner to create new enzymes, thereby amplifying the activation cascade. The common terminal pathway is the formation of the membrane attack complex (C5b-9).

### 2.7. Adaptive immunity

The adaptive immune responses manifest exquisite specificity for their target antigens. The adaptive immunity includes both [1] humoral immunity component by the B cells and [2] cell-mediated immunity component, mediated by T cells. Innate and adaptive immunity usually act together by APC, with the innate response representing the first line of host defence, and with the adaptive response becoming prominent later, as pathogen-specific T and B cells have undergone clonal expansion.

T cells are produced in the thymus and recognise antigens through their highly specific antigen receptors. Mature T cells that have not yet interacted with their antigens are known as naïve T cells. In order to participate in an adaptive immune response, a naïve T cell must first interact with an antigen to initiate an appropriate proliferation and differentiation into effector T cells of contributing to the removal of the antigen, and formation of long-lived memory T cells that rapidly respond to a previously encountered pathogen [40]. The way in which a T cell first encounters antigen largely dictates how it will react subsequently.

Antigen presentation is crucial in initiating and maintaining an appropriate immune response to antigen. A wide range of cells can present antigen, depending on how and where the antigen is first encountered. In a lymphoid organ, there are three main types of professional APCs: dendritic cells, macrophages and B cell. All of these cells exhibit class I and class II major histocompatibility complex (MHC) molecules, which are required for the T cell receptor to recognise processed antigen. Antigen-specific recognition of the peptide in the MHC molecule by the T cell receptor provides the specificity of the interaction, and results in prolonged cell-cell contact.

The effector T cells fall into three functional categories that detected peptide antigens derived from different type of antigen. Intracellular endogenously synthesised molecules such as viruses are presented on MHC class-I molecules to $CD8^+$ cytotoxic T cells while exogenous peptides, derived from extracellular source such as microbes, are presented on MHC class II molecules to $CD4^+$ T helper cells. The $CD4^+$ T helper cell can further differentiate into Th1, Th2 and Th17. Th1 differentiation is elicited in response to infection by intracellular pathogens. They promote cell-mediated inflammatory responses through inducing the activation of macrophages, natural killer cells, $CD8^+$ cytotoxic T cells. However, extracellular antigens tend to stimulate the production of Th2 cells. Th1 cells activate and induce B cells to produce IgG antibodies that are effective in opsonisation. Th2 cells initiate the humoral immune response by activating naïve B cells to produce IgM antibodies, and subsequently induce the production of other isotypes, such as IgA, IgE and IgG [41]. B cells also take up antigen and present it to the T cells, receiving signals from the T cells to divide and differentiate into antibody-forming cells (plasma cells) and memory B cells.

## 3. Immunologically mediated oral diseases

### 3.1. Angioedema

Angioedema (angioneurotic oedema) is localised subcutaneous (or submucosal) and non-pitting swelling, which results from increased extravasation of fluid into interstitial tissues of the respiratory and gastrointestinal tract [42]. Angioedema can be classified into at least eight types, hereditary angioedema, acquired C1 inhibitor deficiency, inherited angioedema with normal C1 inhibitor levels, ACEI-associated angioedema, idiopathic angioedema, allergic angioedema, NSAID-associated angioedema, and angioedema with urticarial vasculitis [43]. The most common sites are periorbital area and lips, followed by tongue, glottis, genitalia, and extremities [44].

### 3.2. Idiopathic angioedema

Idiopathic angioedema can be defined as recurrent, unpredictable and localised swelling of the cutaneous and mucosal tissue without a clear aetiology [45]. It can occur at any age, but is common in the 40–50-year-old [46]. A daily antihistamine may be required [47]. Steroid therapy is effective, but the risks of chronic therapy usually outweigh the benefits [48].

### 3.3. Allergic angioedema

This is a severe type I hypersensitivity reaction (mediated by IgE) that can cause acute angioedema and urticaria. The most common causes of allergic angioedema are medications (aspirin, NSAIDs, antihypertensives, Narcotics, and oral contraceptives), food (nuts, eggs, shellfish, soy, wheat and milk), and others (venom and latex) [49,50]. Antihistamine and steroids can improve the symptoms during an acute episode [48].

### 3.4. Angiotensin-converting enzyme inhibitors (ACEIs) associated angioedema

ACEIs are widely used antihypertensive medication. ACEIs associated angioedema is a rare but potentially fatal adverse effect. Angioedema occurs in 0.1–0.7 % of the patients receiving ACEIs, and they are the number one cause of acute angioedema in the hospital [51]. The onset of the swelling usually occurs within minutes to hours and then resolves in 24–72 h. However, some cases may occur suddenly even though the drug has been well tolerated for months [52,53]. The angioedema seems to be facilitated by ACEIs in predisposed patients rather than causing it [46]. The management includes discontinue ACEIs, airway monitoring (if mouth or throat involvement), and acute symptomatic supportive therapy. There are some therapies, such as C1 inhibitor concentrate, ecallantide, icatibant and possibly fresh frozen plasma might be useful in ACEIs associated angioedema, but available studies are conflicting [54–56].

### 3.5. Hereditary angioedema (inherited C1 inhibitor deficiency)

Hereditary angioedema is an autosomal-dominant condition that characterised by recurrent attacks of self-limiting oedema. There are three types. Type 1 (80–85 %) is the most common (80–85 %) and is characterised by an insufficient production of C1 inhibitors [57]. Patients with type II have a normal amount of C1, but the protein is dysfunctional. Type III is characterised by normal C1 inhibitor and normal complement protein levels. Some of the cases are caused by mutation of F12 gene, which codes for factor XII to activation by plasmin, in other cases the cause is caused by plasminogen, angiopoietin1, kininogen1, MYOF, HS3ST6 or unknown [58].

### 3.6. Acquired angioedema (C1 inhibitor deficiency)

Acquired angioedema is a rare condition that is thought to be autoimmune [57]. Type 1 is associated with lymphoproliferative disorders and occurs via consumption of the C1 inhibitors by the malignant cells. Type 2 is caused by autoantibodies to the C1 inhibitors. However, in some cases, it is hard to distinguish between AAE types 1 and 2 [59]. Treatment of underlying lymphoproliferative disorder is often curative in type 1. Type II has been treated with immunosuppressive.

## 4. Immune-mediated dermatologic diseases

### 4.1. Pemphigus vulgaris

Pemphigus vulgaris is not completely comprehended. It is thought to be triggered when a person with a genetic predisposition to develop this condition is exposed to an environmental stimulus, such as a chemical or a substance [60]. Pemphigus vulgaris is a serious chronic autoimmune disease characterised by epithelial blistering affecting mucocutaneous surfaces. Painful oral erosion usually precedes the onset of skin blisters by weeks or months. The most common sites are the scalp, face, axillae and oral cavity. Patients have autoantibodies against desmoglein-1 and desmoglein-3, which form the junctions between epithelial cells, resulting in the loss of adhesion between the cells. The diagnosis is based on clinical manifestations and confirmed by histological and direct immunofluorescence. Circulating IgG antibodies against the epithelial cell can be detected by indirect immunofluorescence. However, these autoantibodies can be detected in 75 % of the patients with active disease [29]. Systemic glucocorticoids in high dose are still the mainstay therapy. However, because of the potential toxicity of systemic glucocorticoids, (adjuvant therapy) steroid-sparing medication may be initiated long term. The most commonly used are cyclophosphamide, azathioprine, and mycophenolate mofetil [61].

### 4.2. Mucous membrane pemphigoid

Mucous membrane pemphigoid (MMP) is a rare chronic subepithelial immunologically medicated vesiculobullous condition [62]. It is characterized by the production of autoantibodies against the basement membrane zone antigens. Oral mucosa is the most often affected site, followed by skin, ocular conjunctiva, pharynx, external genitalia, nasal mucosa, larynx, anus, and oesophagus [29]. The biopsy reveals a subepithelial bulla with some inflammation. Direct immunofluorescence shows linear deposition of complement and IgG. Serum tests can be used to detect circulating anti-basement membrane zone antibodies (indirect immunofluorescence assay and enzyme-linked immunosorbent assay). Topical corticosteroids can be used in mild localized oral disease or as an adjunct to systemic treatment in patients with more extensive disease. Patients with moderate-to-severe diseases may benefit from systemic agents. Systemic glucocorticoids and dapsone are frequently used to manage MMP. Since long-term side-effect with systemic glucocorticoids, topical therapy or a systemic medication (eg, dapsone, azathioprine, mycophenolate mofetil) is used as a steroid-sparing agent to maintain clinical improvement during and after prednisone tapering [63].

### 4.3. Erythema multiforme

Erythema multiforme is an acute, relatively common immune-mediated condition characterised by serosanguinous exudates on the lips and the appearance of distinctive target-like lesions on the skin. It is considered as a type IV hypersensitivity reaction associated with infections (viral, bacterial, or fungal), with herpes simplex virus (HSV) as the most commonly identified pathogens [64,65]. Mycoplasma pneumoniae infection is commonly seen in children with erythema multiforme [65]. On the other hand, medications have higher aetiological fractions for Stevens-Johnson syndrome and toxic epidermal necrolysis. It is believed that the development of erythema multiforme involves a cell-mediated immune response against viral antigens deposited in lesional skin [66]. Erythema multiforme is diagnosed based mostly on the patient's medical history and physical examination. When required, skin biopsies might aid to confirm the diagnosis.

### 4.4. Oral lichenoid lesion (OLL)

OLL is considered to be a type IV hypersensitive reaction. The exact aetiology of OLL remains unknown. OLL may present as a unilateral lesion, rather than bilateral lesions, which can usually be seen in oral lichen planus (OLP) [67]. OLL may be associated with the use of several dental materials, oral hygiene products, food additives and medications, such as antihypertensives, nonsteroidal anti-inflammatory drugs, anticonvulsants, and antimalarials [68]. The histopathologic features are indistinguishable from idiopathic OLP. The diagnosis of OLL is based on the clinical presentation and the histopathologic features. Direct immunofluorescence may reveal positive staining for fibrinogen, immunoglobulins, and complement.

### 4.5. Graft versus host disease (GvHD)

GvHD is a potential complication of an allogeneic transplant. Acute GvHD is the major cause of early transplant-related mortality, and it occurs within the first day to 100 days post-transplant. Chronic GvHD usually occurs between 100 and 300 days [69]. The clinical signs of GvHD are varied, depending on the organ system involved. Chronic GvHD may represent as a continuation of a previously diagnosed acute GvHD. The chronic oral GvHD may resemble OLP. The tongue, the labial mucosa, and the buccal mucosa are the common sites. The diagnosis of GvHD is made by a tissue biopsy. The histopathologic features resemble those of OLP, however, the inflammation may not as intense as in OLP [70].

### 4.6. Allergic contact cheilitis

Allergic contact cheilitis is an allergic contact dermatitis affecting the lips due to a type IV hypersensitivity reaction following contact with an allergen. It is a relatively common cause of the lip inflammation and most of the patient might have a history of eczema. It is more common in young female than male. Allergic contact cheilitis manifests as eczematous changes on the vermilion borders or skin surrounding the mouth. Lips may appear to be dryness, scaling, and cracking. Some patients may even report the association with itchiness and burning pain of the lip. Determining the allergens that responsible for allergic contact dermatitis requires a full medical history, physical examination, and in some cases, patch testing. The therapy entails avoiding the allergen in all feasible sources. The reaction then usually settles quickly.

### 4.7. Plasm cells gingivitis

Plasma cell gingivitis (PCG) is a rare benign inflammatory condition of gingiva characterised by diffuse and dense infiltration of plasma cells into the connective tissue [70]. The aetiology of PCG remains unknown, but a hypersensitive reaction to allergens has been suggested. Clinically, PCG appears as a diffuse, friable, erythematous and oedematous enlargement of the gingiva, and may extend from the free marginal gingivae on to the attached gingiva. The diagnosis of PCG is made on the basis of histopathological examination. The histology may show the infiltrate of plasma cells in a dense collagenous stroma. Several treatments have been tried, including topical and systemic corticosteroids, and topical fusidic acid. However, no treatment clearly stands out as consistently effective.

## 5. Connective tissue diseases

### 5.1. Systemic lupus erythematosus (SLE)

SLE is the classic autoimmune disease characterised by immune complex deposition (type III hypersensitivity). Variable clinical manifestations are observed in patients, ranging from modest joint and oral/skin involvement to life-threatening renal, hematologic, or central nervous system involvement. The most common presenting symptoms are constitutional, such as fever, fatigue, weight loss, and lymphadenopathy without a focal infection [71]. Other common presenting symptoms include arthralgia and myalgia, which can be migratory or symmetrical [72]. Less common presenting symptoms include photosensitive skin lesions (malar rash), pleuritic chest pain, Raynaud phenomenon, oral lesions, neurologic symptoms, and recurrent miscarriages. Many organ systems may be affected by SLE, necessitating a comprehensive physical evaluation. Laboratory tests (complete blood count, acute phase reactants, urinalysis, serum creatinine and estimated glomerular filtration rate, anti-double-stranded DNA, and complement levels) may be used to help assess disease activity and monitor organ-specific complications. However, as there is no single marker of disease activity, clinicians should interpret the laboratory results in the appropriate clinical context. The diagnosis of SLE is based on the American College of Rheumatology criteria or the Systemic Lupus International Collaborating Clinics classification criteria [73–75].

### 5.2. Granulomatosis with polyangiitis (Wegener granulomatosis)

Granulomatosis with polyangiitis is a multi-system granulomatous vasculitis. The cause is unknown. It is thought to be a type III immune-complex hypersensitivity reaction leads to vasculitis of small-to-medium arteries and veins [76]. Granulomatosis with polyangiitis occurs in two forms: systemic disease (including glomerulonephritis), or a limited form without renal involvement. Both forms typically present with non-specific symptoms, including fever, malaise, anorexia, weight loss, myalgias, and arthralgias [77–79]. The initial evaluation should consist of a comprehensive medical history, physical examination, and laboratory tests. (detection of anti-neutrophil cytoplasmic autoantibody). 95 % of patients will have detectable anti-neutrophil cytoplasmic autoantibody (ANCA), of whom 71–95 % will have c-ANCA, and 10–27 % p-ANCA [80,81]. Additional tests such as complete blood count, acute phase reactants, liver and kidney functions, anti-double-stranded DNA, complement levels, tuberculosis screen, and blood cultures should be performed to exclude alternative diagnoses. Selective imaging may be useful in evaluating patients who are suspected or known granulomatosis with polyangiitis. Suspected active site should be biopsy if possible.

### 5.3. Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder with unknown aetiology. The common presentation features may include bi-hilar lymphadenopathy, erythema nodosum, arthritis, and eye lesions [82]. The formation of non-caseating granulomata is typical, however is not diagnostic. The differential diagnosis of non-caseating granulomata may include infection, foreign body reaction, inflammatory bowel diseases, chronic granulomatous disease, and vasculitis and connective tissue diseases. Typically, the granuloma comprises a central area of macrophage, epithelioid cells, and Langerhans giant cells surrounded by lymphocytes and fibroblasts [70]. No specific diagnostic tests are available for sarcoidosis. Raised serum angiotensin converting enzyme levels in about 75 % of patients [83]. Other tests, such as complete blood count, liver and kidney function, Vitamin D level, acute phase reactants, serum Ig, calcium and urinary calcium excretion, imaging (chest x-ray and/or CT), biopsy and bronchoscopy are useful in making the diagnosis.

### 5.4. IgG4-related disease

IgG4-related disease is a fibro-inflammatory condition that is characterised by dense lymphoplasmacytic infiltrations with a predominance of IgG4-positive plasma cells in the affected tissue with unknown cause [84]. Elevation of IgG4 is not specific to IgG4-related disease, it can be also found in other conditions such as multicentric Castleman's disease and Churg-Strauss syndrome [85,86]. Immune complex deposition (type III hypersensitivity) could be seen in affected tissues such as pancreas and kidneys [87]. Most of the patients with IgG4-related disease have lymphadenopathy. As IgG4-related disease might involve one or multiple organs, and clinical features of this disease have been demonstrated in many every organ system. Investigation requires a combination of clinical, histopathologic, radiological and serological tests. Tissue biopsy may show lymphoplasmacytic tissue infiltration of mainly IgG4-positive plasma cells and lymphocytes, accompanied by storiform fibrosis [88].

## 6. Immunodeficiency disorders

Immunodeficiencies are a group of diseases caused by quantitative and/or qualitative changes in the essential immunologic and metabolic pathway involved in both the innate and the adaptive immune response [89]. They can be classified into primary (genetic defects) and secondary (caused by other diseases) [90]. Immunodeficiencies also can be divided into innate (complement or neutrophils) or adaptive (T cells or B cells) system. Patients with immunodeficiencies should be under the care of clinical immunologist or haematologist.

### 6.1. Primary immunodeficiencies (PIDs)

PIDs are genetically determined, that can lead to mild to life-threatening infections, and autoimmune disorders [91]. PID symptoms manifest during infancy and childhood as recurrent or atypical infection, but some can first occur in adults. General clinical features of

immunodeficiency may include unusually persistent or recurrent infections, infection with unusual germs (e.g. Aspergillus, Pneumocystis), infection with unexpectedly severe, infection of unusual sites, chronic diarrhoea, failure to thrive in infants and children, non-infectious granulomatous disorders, chronic osteomyelitis/deep-seated abscesses, and structural damage (e.g. bronchiectasis) [90].

### 6.2. B-cell disorders

B-cell disorders are most common and include X-linked agammaglobulinaemia (Bruton's agammaglobulinaemia), common variable immunodeficiency (acquired hypogammaglobulinaemia), selective IgA deficiency, IgG subclass deficiency and specific antibody deficiency with normal immunoglobulins [92].

X-linked agammaglobulinaemia is a genetic disorder due to mutations on the X chromosome affecting the Bruton's tyrosine kinase gene [93]. Patient usually presents with recurrent infections of lungs and ears (Haemophilus influenzae and pneumococci) after 6 months of age, when maternal antibody has disappeared. The diagnosis is based on evaluation of serum immunoglobulins, measurement of the B cells, molecular analysis (single-strand confirmation polymorphism, DNA analysis, denaturing gradient gel electrophoresis, or reverse transcriptase polymerase tests on the BTK gene), and the genetic studies [94]. Common variable immunodeficiency is one of the common antibody deficiencies, and in many cases, the aetiology is unknown. Patient usually presents with recurrent bacterial infections, as for X-linked agammaglobulinaemia [95]. The laboratory features include low levels of serum immunoglobulins, including IgG, IgA and sometimes IgM, which causes an increased susceptibility to infection at any age from childhood to old age [96]. Selective IgA deficiency is the most common primary antibody deficiency that is characterised by an undetectable level of IgA in the blood and secretions [97]. Most cares are asymptomatic, but some patients develop various clinical manifestations such as pulmonary infections (Haemophilus influenzae and Streptococcus pneumoniae), allergies (allergic conjunctivitis, rhinitis, urticaria, eczema, food allergy and asthma), autoimmune diseases (SLE, rheumatoid arthritis, and juvenile rheumatoid arthritis), gastrointestinal disorders (coeliac disease and inflammatory bowel disease) and malignancy (B cell lymphoma) [98]. Based on the European Society for Immunodeficiencies, the diagnosis requires the demonstration of undetectable IgA in the presence of normal IgG and IgM levels at an age older than 4 years in whom other causes of hypogammaglobulinemia have been excluded [99]. IgG subclass deficit is characterised by a substantial reduction in the blood concentrations of one or more IgG subclasses in a patient with a normal overall IgG concentration and an unexplained aetiology [100]. Clinically, IgG subclass deficiency may be asymptomatic or associated with recurrent infections [101]. The initial evaluation is based on the clinical history, examination and laboratories including complete blood count and differential, serum immunoglobulins, IgG subclasses, antibody titres to proteins and polysaccharide antigens, and total haemolytic complement and alternative haemolytic complement [102]. Patient should be referred to clinical immunologist and haematologist for further evaluation. Specific antibody deficiency with normal immunoglobulins is characterised by a failure to respond to polysaccharide antigens in an individual with normal responses to protein antigens, normal serum levels of immunoglobulins. The cause is unknown. Recurrent bacterial infection of upper and lower respiratory tract is common [103,104]. The initial evaluation may include history, examination and laboratory studies (serum levels of IgG, IgA, and IgM, IgG subclass levels, and assessment of response to polysaccharide and protein vaccines) [105,106]. Patient should be referred to clinical immunologist and haematologist for further evaluation.

### 6.3. T-cell disorders

Primary T-cell disorders are rare and include DiGeorge syndrome (22q11.2 deletion syndrome), Wiskott-Aldrich syndrome, ataxia telangiectasia, chronic mucocutaneous candidiasis, idiopathic CD4 lymphopenia, autoimmune lymphoproliferative syndromes, Cartilage-Hair Hypoplasia and other chromosomal breakage syndromes [107–114]. The presentation of T-cell disorders is highly variable among causes, but generally primary T-cell disorders might manifest as unusually severe common upper and lower respiratory tract infection (viral, bacterial or fungal), chronic diarrhoea, atopic dermatitis, failure to thrive [115].

### 6.4. Phagocytic cell defects

Phagocytic cell defects are not common. Defects of neutrophil differentiation (neutropenia), deficiencies of motility, and disorders of respiratory burst are the main types. The common phagocytic defects are myeloperoxidase deficiency, chronic granulomatous diseases, cyclic neutropenia, and glucose-6-phosphate dehydrogenase deficiency.

Myeloperoxidase deficiency is an autosomal recessive inherited disorder, and the most common primary phagocytes disorder. The majority of patients are asymptomatic. Defects in killing Candida albicans and Aspergillus fumigatus were reported [116,117]. Chronic granulomatous disease is the most significant phagocytes defect (neutrophils and monocytes) and is characterised by defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex [118]. Patients with chronic granulomatous disease usually present with recurrent or severe bacterial or fungal infections, and they are prone to the formation of granulomata. Cyclic neutropenia is a rare autosomal dominant condition that is characterised by cyclic reductions in neutrophils. This disorder is due to mutations in the ELANE gene, encoding neutrophil elastase. Typical cases of cyclic neutropenia have oscillations of neutrophils and monocytes from 14 to 35 days [119]. Patients usually present with a history of recurrent fevers, mouth ulcers, and infections. The diagnosis is confirmed by serial blood counts with differential (three times weekly over four weeks) [90] and detecting of a heterozygous pathogenic variant of ELANE. Glucose-6-phosphate dehydrogenase deficiency (G6PD) is an X-linked condition that is caused by a genetic defect in the red cell enzyme G6PD, which impairs the NADPH system of oxidative metabolism. In patients with G6PD, haemolytic anaemia could occur after eating certain foods (fava beans) and drugs (dapsone, salicylates, primaquine, cotrimoxazole, sulfadiazine and quinolones) [120].

### 6.5. Secondary immunodeficiency

Secondary immunodeficiencies are far more common than primary immunodeficiencies, and some of secondary immunodeficiencies have become global health issues [121]. They are commonly caused by immunosuppressants, infections, age extremes, malnutrition and metabolic disorders, genetic defects other than primary immunodeficiencies, trauma, burns, major surgery, haematological neoplasia, environmental conditions [122–124] (Table 1). The secondary immunodeficiencies have a broad range of presentation, depending on the magnitude of the offending extrinsic cause and on the host susceptibility [125]. These are transient and usually less severe than the immunodeficiency seen in AIDS. For example, the immunodeficiency induced by immunosuppressive agents depends on the dose used [126]. Infections with measles virus, cytomegalovirus, and influenza virus could induce transitional lymphopenia; however, HIV-1 and HIV2 are retroviruses, responsible for the acquired immunodeficiency syndrome, which could cause severe immunodeficiency if not treated [127]. However, protein-calorie malnutrition (under or over) is the most common cause of immunodeficiency [128,129]. The deficiency of micronutrients such as zinc and ascorbic acid might lead to increased susceptibility to infections via the weakening of mucosa, therefore facilitating a pathogen's invasiveness [127,130]. Vitamin D is essential for macrophage activity against intracellular pathogens [131]. The treatment of secondary immunodeficiencies is generally achieved with the management of the primary condition or the removal of the offending agent [132].

**Table 1**
Causes of secondary immunodeficiencies [90,132].

| Infections | Tumours | Medical condition | Malnutrition | Drugs and toxins | Physical therapies and surgery | Extremes of age | Environmental conditions |
|---|---|---|---|---|---|---|---|
| Viral (HIV, CMV, EBV)<br>Septicaemia<br>Chronic bacterial and parasitic infection (TB, leishmaniasis) | Plasma cell tumours and related problems<br>Lymphoma/ leukaemia | Chronic renal disease<br>Gastrointestinal disease<br>Diabetes mellitus<br>Cilial dyskinesia<br>Cystic fibrosis<br>Yellow nail syndrome<br>Young syndrome<br>A-1-antitrypsin deficiency<br>Burns<br>Myotonic dystrophy | Undernutrition<br>Overnutrition | Immunosuppressants<br>Cytotoxic agents<br>Chemicals | Radiotherapy<br>Plasmapheresis<br>Splenectomy<br>Cardiac surgery | Prematurity<br>Advanced age | UV light<br>Radiation<br>Hypoxia<br>Space Flight |

## 7. Dental consideration

Dental professionals should be aware of the oral manifestations of immunodeficiencies, so that early diagnosis can be made and treatment can be started promptly. Improving awareness of the oral manifestations of immunodeficiencies is an important step in preventing underdiagnosis and delayed diagnosis, can reduce disease or treatment complications, improve patient prognosis, improve the quality of life on patients and their families, and reduce the socioeconomic burden of the disease [133–135]. Patients with immunodeficiency disorder have an increased susceptibility to dental diseases, including caries, periodontitis, and tooth loss. A comprehensive preventive program is of primary importance in meeting their dental needs. The teeth, gingivae, and tongue should be cleaned at least twice daily. The use of electric toothbrushes is advised. Fluorinated toothpaste should be used, and in places where water fluoride levels are not optimum, a prescription high-dose fluorinated toothpaste should be considered for people prone to dental cavities. Furthermore, flossing should be done at least once a day. Sugary beverages have to be avoided. Sugar-free gum may be advantageous. Immunodeficiency condition patients do not often need antibiotic prophylaxis for standard dental procedures.

## 8. Conclusion

The oral manifestations of both local and systemic disease make the oral cavity an important part of the immune system. A thorough examination of the oral cavity may show signs of an underlying systemic disorder, allowing for early diagnosis and therapy. Dentists need to be familiar with the range and number of immune-mediated conditions that can present with initial or even isolated oral manifestations given their potential for morbidity, the poor quality of life of affected patients, and their potential mortality.

## Declaration of Competing Interest

The authors declared that they have no conflict of interest.

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