Published in final edited form as:

Oral Dis. 2017 October ; 23(7): 866–888. doi:10.1111/odi.12584.

PERIODONTAL AND OTHER ORAL MANIFESTATIONS OF IMMUNODEFICIENCY DISEASES

Mark E Peacock, DMD, MS^{*}, Roger M. Arce, DDS, MS, PhD[†], and Christopher W Cutler, DDS, PhD[‡]

^{*}Associate Professor, Departments of Periodontics, Oral Biology

[†]Assistant Professor, Departments of Periodontics, Oral Biology

[‡]Professor, Departments of Periodontics, Oral Biology; Chair, Department of Periodontics, Associate Dean for Research, The Dental College of Georgia at Augusta University

Abstract

The list of immunodeficiency diseases grows each year as novel disorders are discovered, classified, and sometimes reclassified due to our ever-increasing knowledge of immune system function. Although the number of patients with secondary immunodeficiencies (SIDs) greatly exceeds those with primary immunodeficiencies (PIDs), the prevalence of both appears to be on the rise probably because of scientific breakthroughs that facilitate earlier and more accurate diagnosis. Primary immunodeficiencies in adults are not as rare as once thought. Globally, the main causes of secondary immunodeficiency are HIV infection and nutritional insufficiencies. Persons with acquired immune disorders such as AIDS caused by the Human Immunodeficiency Virus (HIV) are now living long and fulfilling lives as a result of highly active antiretroviral therapy (HAART). Irrespective of whether the patient's immune deficient state is a consequence of a genetic defect or is secondary in nature, dental and medical practitioners must be aware of the constant potential for infections and/or expressions of autoimmunity in these individuals. The purpose of this paper is to review the most common conditions resulting from primary and secondary immunodeficiency states, how they are classified, and the detrimental manifestations of these disorders on the periodontal and oral tissues.

Keywords

autoimmune disease; immune defects; autoinflammatory diseases; periodontium; immunopathology

INTRODUCTION

Patients with compromised immune function are predisposed to a variety of systemic and oral manifestations, including inflammation of the periodontium and surrounding tissues

Correspondence should be addressed to the following: Christopher W Cutler, DDS, PhD, Professor and Chair, Department of Periodontics, The Dental College of Georgia at Augusta University, 1120 15th Street, GC-1335, Augusta, Georgia 30912, Phone: 706-721-2442, Fax: 706-723-0215, chcutler@augusta.edu.

Conflict of Interest: None.

(Szczawinska-Poplonyk et al., 2009). As the life expectancy grows for many of these patients thanks to advanced therapeutic modalities, oral health care providers will no doubt have to take on more responsibility in the treatment of this expanding population (Atkinson et al., 2000). Immunocompromised patients often have complex multifactorial histories requiring dental personnel to understand the primary disease processes and to coordinate care with medical specialists. The patients survival followed by Improvement of quality of life is the essential goal. The number of primary immunodeficiencies (PIDs) and conditions that can lead to secondary immunodeficiencies (Verma et al.) is extensive, and all cannot be expounded upon in this format. We start with a brief overview of the immune system.

Immunodeficiency relates to the body's immune system being unable to perform its normal functions in protecting the host. Primary immunodeficiencies are hereditary (genetically conferred by progeny); whereas secondary immunodeficiencies are acquired. Secondary immunodeficiencies are much more common, as they relate to other systemic disorders (eg, diabetes, undernutrition, HIV infection) or immunosuppressive treatments (eg, cytotoxic chemotherapy, bone marrow ablation before transplantation, radiation therapy). Understanding the basic concepts of how the immune system works helps to appreciate a specific disorder and the component(s) that it affects. A general outline of the immune system is shown in Figure 1. This is not meant to be an all-inclusive guide to the cellular immune system. Innate immunity includes phagocytic cells (neutrophils, dendritic cells and macrophages); with both dendritic cells and macrophages being antigen-presenting cells, APCs). Also part of the innate immune system are natural killer (NK) cells, and complement. The adaptive immune system incorporates T-cells and B-cells. Crucial to bridging innate and adaptive immunity are APCs, especially dendritic cells, the sole mediators of initiating the adaptive immune response by promoting clonal expansion of naïve T-cells.

INFLAMMATORY CELL INFILTRATE IN CHRONIC PERIODONTITIS: FORMATION OF ORAL LYMPHOID FOCI

The inflammatory cells that infiltrate the periodontal tissues of humans with gingivitis and periodontitis have recently been more clearly defined and should be reiterated here (Jotwani et al., 2001, Jotwani & Cutler, 2003, Jotwani et al., 2004). These findings were the result of using new antibodies, particularly those against dendritic cell subsets and T cell subsets. The earliest inflammatory response to plaque biofilm consists largely of neutrophils, which migrate through from the lamina propria, to the junctional epithelium out into the gingival crevice. This neutrophil efflux persists throughout the disease process. Langerhans cells and $\gamma\delta$ -T cells inhabit the gingival/crevicular epithelium, with Langerhans cells increasingly being mobilized through the basement lamina in gingivitis and periodontitis (Jotwani & Cutler, 2003). Langerhans cells become double positive for CD1a and CD83 in the lamina propria in periodontitis, indicative of an active maturation process. Dermal dendritic cells, macrophages, B cells and CD4+ and CD8+ T cells predominantly infiltrate the lamina propria. Established advanced periodontitis is characterized by the formation of DC-CD4+ T cell immune synapses, which we have termed oral lymphoid foci (OLF) (Jotwani & Cutler,

2003). OLF have been illustrated previously and will be reiterated here (Cutler & Jotwani, 2006).

PRIMARY IMMUNODEFICIENCIES (Genetic)

Since 1973 the Expert Committee on Primary Immunodeficiency of the International Union of Immunological Societies (IUIS) has described and classified primary immune defects, the most recent discussion having been published in 2014 (Al-Herz et al., 2014). There are over 250 recognized primary immunodeficiency disorders (Fuleihan & Etzioni, 2012), and they are grouped into nine major categories with several conditions belonging to more than one category (Table 1). Many of these illnesses are uncommon and attempts to classify them can be fairly subjective. The features and manifestations of each PID are itemized in Table 2. Table 3 lists the PIDs that are associated with plaque-versus non-plaque-related conditions, as well as the PIDs that have no known association with periodontal disease. The frequency of primary immune deficiency detection is rising, especially in older adults (Verma et al., 2013), with an overall incidence of approximately 1 in 1200 (Boyle & Buckley, 2007, McCusker & Warrington, 2011). Rapid advances in cell and molecular genetics are furthering the ability to promptly diagnose and treat many of these diseases.

1. Combined Immunodeficiencies (CID)—These disorders, CID without nonimmunologic phenotypic abnormalities, are characterized by decreased numbers of T-cells (T^+B^+) and often a reduction in B-cell count (T^+B^-). Genetic defects that result in small numbers of T-cells will invariably produce fewer activated B-cells, and therefore diminished immunoglobulin (Ig) production. CD40 Ligand Deficiency (previously Hyper-IgM Syndrome) is classified in this category as well as in the Predominantly Antibody Deficiencies grouping. The rationale for this dual classification is because in the past the major feature of this PID was defective switching from IgM (IgM is increased or normal, other isotypes are decreased) to other isotype classes. It is now known that the CD40 protein on APCs is necessary for proper dendritic cell signaling and promotes B-cell activation and isotype switching. CD40L deficiency is currently recognized to be a defect of co-stimulatory T-cell function, thus the classification in two groups.

Severe Combined Immunodeficiency (SCID)

Pathogenesis: This group consists of many genetic variations of the most severe types of CID, represented by little or no T- and B-cells and defective antibody responses. Typical SCID patients usually have less than 500 circulating CD3 T-cells (Roifman et al., 2012), and SCID is the most severe of all the PIDs. Defective interleukin (IL) receptors and IL receptor pathways can prevent the proper development of T-cells. Recent evidence has shown that some of these defects permit T-cell development, but compromise their cellular function by disrupting certain steps in intracellular signaling (Notarangelo, 2013). X-linked (XL) SCID comprises approximately half of all SCID cases, and is manifested by a mutation of the cytokine receptor common gamma chain (γC) subunit (IL2RG, γC encoded by gene for IL2 receptor located on X chromosome) (Fischer et al., 2005). Besides IL2, the subunit protein is also shared by IL4, 7, 9, 15 and 21, and is necessary for the growth and differentiation of T-cells, NK-cells, and B-cells. The end result is a failure of the immune system to develop. Invariably, this disease is fatal within the first two years of life unless the immune system is

reconstituted (Allenspach et al., 1993). The two most common forms of SCID are X-linked (passed on by the mother) and the autosomal recessive (AR) Adenosine Deaminase (ADA) Deficiency. ADA deficient SCID is the second most common form of SCID, and was the first PID in which the molecular defect was identified (Blackburn & Thompson, 2012). ADA is an enzyme necessary for the breakdown of purines, specifically converting adenosine to inosine and deoxyadenosine to deoxyinosine (Perez-Aguilar et al., 2012). Without ADA, adenosine builds up and leads to an increase in metabolites (such as dATP) that are lethal to lymphocytes. This underscores the importance of purine metabolism in immune system maturation. Other associated features include costochondral junction flaring, hearing impairment and neurological features.

Treatment: The earlier that these patients receive treatment after birth, the better their rate of survival. Treatment consists of Hematopoietic Cell Transplantation (HCT) or retroviral vector gene therapy in those patients who cannot have bone marrow transplants or have previously failed to respond to HCT. Survival after HCT with HLA-identical donors has been reported to be over 92% (Grunebaum et al., 2006). In candidate patients for transplantation, HCT therapy has increased survival rates for SCID patients from 23% to over 90% in the last 40 years (de la Morena & Nelson, 2013). High-resolution DNA donor-recipient matching and enhanced conditioning regimens have contributed to these therapeutic achievements. In fact, ADA deficient SCID was the first congenital disease to be treated by gene therapy (Blackburn & Thompson, 2012), and long-term studies have shown a permanent cure with HCT if the patient endured the transplant therapy (Hassan et al., 2012). As with X-linked SCID, ADA deficient SCID patients are predisposed to opportunistic infections of the same types.

Oral manifestations: Oral and periodontal manifestations for untreated individuals in their first year include candidiasis, viral infections, and ulcerative stomatitis (Porter & Scully, 1994, Stocks et al., 1999).

MHC (major histocompatibility complex) Class I and II Deficiency (Bare Lymphocyte Syndrome)

Pathogenesis: MHCs are cell surface molecules vital to proper lymphocyte development and function. They are also called human leukocyte antigens (HLA) in humans. MHC I is found on all cells except red blood cells, and MHC II is located on B-cells and APCs, in particular dendritic cells. MHC I molecules are needed for CD8 T-cell expression and MHC II particles present antigens to CD4 cells. MHC II Deficiency patients are susceptible in their first year or two of life to severe infections, mainly viral infections, which are the major cause of death (Cole & Cant, 2010, Guirat-Dhouib et al., 2012). Other associated features include vasculitis, pyoderma gangrenosum, respiratory tract infections and liver tract disease.

Treatment: Overall, the treatment for this disease is usually focused to alleviate symptoms. There is no real cure for MHC Class I deficiency, and gene therapy at this time is not possible due to the presence of MHC I molecules on nearly all cells (nucleated cells). Stem cell transplantation is presently the only chance of treatment, although some studies show a

more negative survival outcome than with SCID because of increased chance of graft rejection (Saleem et al., 2000). This can occur because in MHC II patients, there is enough remaining host immunity to reject the graft without preconditioning (Small et al., 2013). Patients with MHC I Deficiency can present with serious bacterial infection of usually the respiratory tract, but can also frequently be asymptomatic (Zimmer et al., 2005). MHC I deficient patients do not exhibit the severe viral infections seen in MHC II patients, possibly due to normal antibody production with Class I Deficiency. MHC II deficient individuals frequently demonstrate hypogammaglobulinemia as the decreased CD4 cell number does not allow T-cell dependent activation of B-cells.

Oral manifestations: No reports in the literature describe specific oral complications of MHC I Deficiency, although chronic sinusitis and post-nasal drip often progresses to severe lung infection in this group of patients (Gadola et al., 2000). However, oral herpetic infection is often present.

2. Combined Immunodeficiencies (CID) with Associated or Syndromic

Features—This class of disorders has deficiencies similar to CIDs, although CID with syndromic features predominantly affect T-cells. Patients in these categories are susceptible to persistent infections and their life expectancy is reduced. The number of circulating B-cells is usually near normal. The incidence for these diseases is uncommon, except for DiGeorge Syndrome. Botto et al found an incidence of 1 in 5950 births for DiGeorge's (Botto et al., 2003).

DiGeorge Anomaly (Chromosome 22q11.2 Deletion Syndrome)

Pathogenesis: Also known as Deletion 22 Syndrome, this disorder can be inherited or more commonly found (>90%), as a consequence of a *de novo* defect (environmental?). It is the most common chromosomal deletion abnormality (Gennery, 2012). Most cases have a thymic deficiency, and many also display hypoparathyroidism which may predispose them to seizures from low calcium. Over 80% of DiGeorge patients have cardiac defects (Botto et al., 2003), although many show different organ system involvement. The T-cell deficit may subject patients to opportunistic infections, although this usually improves with age provided their other organ system defect(s), especially heart defects, is/are corrected. Distinguishing maxillofacial/head and neck defects, besides thymic, thyroid, and parathyroid abnormalities, include laryngeal, pharyngeal, esophageal, tracheal, and cleft palatal deformities (Marom et al., 2012).

Treatment: Early diagnosis and treatment directed at affected organ systems leads to more favorable outcomes.

Oral manifestations: Malformations in dental anatomy, enamel (hypoplasia), missing teeth, dental eruption patterns, and caries are seen frequently (Klingberg et al., 2002). Nordgarden et al discovered more enamel hypomineralization than hypoplasia, and this finding was not correlated to patients' medical conditions (Nordgarden et al., 2012).

Ataxia-Telangiectasia

Pathogenesis: A-T is a DNA Repair Defect where the mutation is on the ataxia-telangiectasia mutated (ATM) gene. The ATM protein kinase activates other proteins responsible for cell cycle regulation, DNA breakage repair, and apoptosis. This disorder affects multiple organ systems, particularly the nervous and immune systems, and these patients have a high predisposition to malignancies. Individuals suffer from movement coordination (ataxia), ocular telangiectasia, frequent infections (specially pulmonary), and an elevated incidence of leukemias and lymphomas (Gatti, 1993). There is a progressive decrease in T-cells and often a reduction in IgA, IgE, and IgG (Al-Herz et al., 2011). Neurologic decline is progressive and there is no treatment that is definitive for this disease.

Treatment: Therapy is mainly supportive in nature, and the long-term prognosis for most is grim. Micol et al revealed an overall 20-year survival rate of 53.4%, a prognosis that has not changed in almost sixty years (Micol et al., 2011).

Oral manifestations: Reports of periodontal manifestations are sparse, but increased rates of recurrent herpetic gingivostomatitis and candidiasis have been described (Cohen et al., 1984).

Wiskott-Aldrich Syndrome (WAS)

Pathogenesis: WAS is a rare XL disorder arising from an alteration in the WAS protein (WASP) gene that involves between 1 and 10 persons per million (Catucci et al., 2012). It affects primarily males, although there are instances in the literature linking WAS to females (Lutskiy et al., 2002). WASP, expressed exclusively on hematopoietic stem cells, is a signaling molecule that controls actin cytoskeletal (polymerization) formation, and sustains viability of the immunological synapse (Notarangelo et al., 2008). WASP deficiencies affect the immune response, cell motility, and protection against autoimmune diseases. T-cells are decreased and IgM production is decreased. IgA and IgE are often decreased (Al-Herz et al., 2011). Clinical features associated with WAS are microthrombocytopenia (decreased number and size of platelets), eczema, malignancies (lymphoma), recurrent bacterial and viral infections, IgA nephropathy, and a high incidence of autoimmunity (Massaad et al., 2013). Severe refractory thrombocytopenia early in life has been shown to be connected to a life-threatening outcome (Mahlaoui et al., 2013). As with many other PIDs that affect T/B-cell function, WAS patients have an elevated predisposition to autoimmune diseases. Between 22–72% of WAS patients develop autoimmune illness, and the most frequent condition is hemolytic anemia (Catucci et al., 2012).

Treatment: The treatment of Wiskott–Aldrich syndrome is currently limited on correcting symptoms. However, hematopoietic stem cell transplants and/or lentivirus gene therapy have been reported and described as promising (Malech & Ochs, 2015).

Oral manifestations: Periodontal manifestations described are gingival ulceration with bleeding tendency and palatal petechiae (Boraz, 1989, Porter et al., 1994). Stem-cell gene therapy as early as possible is the treatment of choice (Boztug et al., 2010).

Hyper IgE Syndromes

Pathogenesis: HIES are rare PID disorders, found in either an autosomal dominant (AD) HIES type (Job's Syndrome) or one of several autosomal recessive (AR) HIES forms. The exact prevalence is not known, however there are only roughly 200 cases reported in the literature (Yong et al., 2012). AD-HIES is due to a mutation in the STAT3 (signal transducer and activator of transcription 3) protein gene, and most occurrences of AR-HIES are a result of a DOCK8 (dedicator of cytokinesis 8) gene defect (Heimall et al., 2010). STAT3 is key for cellular communication that is important for cell growth, chemotaxis, and apoptosis, while DOCK8 is fundamental to intracellular signaling. AD-HIES patients exhibit reduced Th17 (T helper) CD4 cells, whereas AR-HIES patients present with reduced T-cells (more so CD8 than CD4) and normal or reduced B-cells. All inherited forms of HIES express elevated IgE. Distinguishing features associated with AD-HIES are connective tissue and skeletal abnormalities to include maxillofacial irregularities and a prominent arched palate, recurrent skin and pulmonary infections (eczema, pneumatoceles), recurrent fungal infections, prolonged healing of infections, retained and/or delayed shedding of primary teeth, and ligneous gingivitis/periodontitis (destructive membranous periodontal disease) (Freeman et al., 2009, Aldous et al., 2007, Deepa et al., 2012, Hatori et al., 1993, Gunhan et al., 1999, Sivoilella et al., 2012, Grimbacher et al., 1999, Gunhan et al., 1994). Grimbacher et al revealed that over 70% of their studied patient population with HIES had retained primary dentition (Grimbacher et al., 1999). AR-HIES types do not display the skeletal and connective tissue abnormalities seen with AD-HIES, nor do they appear to endure the same oral manifestations observed in AD-HIES.

Treatment: Treatment for HIES can be supportive, but HCT therapy is usually curative.

Oral manifestations: Ligneous periodontal disease, an accumulation of fibrin in tissues as a result of a plasminogen deficiency, has recently been associated with HIES (Gunhan et al., 1999).

Dyskeratosis Congenita (DKC)

Pathogenesis: DKC disorders are rare inherited syndromes that can be XL, AR, or AD. They are a multifaceted group of diseases clinically typified by skin hyperpigmentation, pancytopenia (produced by an increase in hemophagocytic activity), premalignant oral leukokeratosis, dystrophic nails, and recurrent infections (Al-Herz et al., 2011, Savage & Bertuch, 2010). DKC is a condition of telomerase shortage caused by mutations in any one of nine (as of this date) telomeric protein genes (Ballew & Savage, 2013). Telomerase activity is vital for the repair and maintenance of cells, especially in highly replicating tissues such as hematopoietic and/or dermatological cells. A decrease in telomerase will result in shortened telomeres on chromosomes, leading to multiple system disease expression. Circulating T-cells, B-cells, and serum Ig can be decreased or variable, and bone marrow failure, liver disease, pulmonary fibrosis, and aplastic anemia (86% of time) are frequently observed (Mialou et al., 2013). Signs and symptoms may not be seen until later in childhood or early adulthood.

Treatment: Optimal treatment for DKC patients is HCT from matched donor(s).

Oral manifestations: Oral, dental, and periodontal manifestations reported are leukoplakia, decreased dental crown to root ratio, tooth taurodontism, and early-onset aggressive periodontal disease (Atkinson et al., 2008, Wald & Diner, 1974, Yavuzyilmaz et al., 1992). Atkinson et al detected oral leukoplakia in 65% of their study population, predisposing these individuals to oropharyngeal carcinoma (Atkinson et al., 2008).

Schimke Syndrome (SIOD)

Pathogenesis: SIOD (Schimke Immune-Osseous Dysplasia) is a very rare PID that affects multiple systems. It is autosomal recessive caused by a mutation in the SMARCA1 gene, a protein involved in chromatin binding and remodeling (5). Patients with SIOD are characterized by short stature, progressive renal disease, decreased T-cells, recurrent lymphopenia, spondyloepiphyseal dysplasia (SED), and facial dysmorphism. Other conditions sometimes seen are hyperpigmentation, hypothyroidism, atherosclerosis, cerebral ischemia, microcephaly, and bone marrow failure.

Treatment: Treatment for SIOD patients includes symptomatic as needed, kidney transplantation, bone marrow transplantation, hip replacement surgery, antimicrobial medications, and anticoagulant therapy. Average age of mortality is around 10 years, although some have survived into their fifth decade of life (Morimoto et al., 1993).

Oral manifestations: Dental anomalies reported include microdontia, hypodontia, short and thin tooth roots, and malformed primary and/or permanent molars (Morimoto et al., 2012, Gendronneau et al., 2014). Morimoto et al were the first to scientifically investigate the oral defects associated with SIOD (Morimoto et al., 2012).

3. Predominantly Antibody Deficiencies—Antibody deficiencies are by far the most common group of all PIDs (Fried & Bonilla, 2009), with over half of all PIDs associated with reduced/absent Ig or normal/increased Ig that is dysfunctional. B-cell numbers may be decreased, absent, or even normal. Common variable immunodeficiency disorders (CVID), the most frequent symptomatic IDs, and IgA deficiencies, the most common of all IDs, are disorders categorized in this group (Fuleihan & Etzioni, 2012). Core treatment for antibody deficiencies in most patients is Ig replacement therapy, either intravenous (IV) or rapid push subcutaneous (SC) (Ballou, 2008). Local adverse reactions are rare with IV, but are observed in 75% of patients receiving SC Ig (Stiehm, 2013). Conversely, a significant proportion of patients (20–50%, 5–15% of all infusions) endure adverse systemic effects with IV, but not with SC (Stiehm, 2013). Although SC allows for simplicity and convenience over IV, both methods are equally effective and neither technique has been shown to be better than the other (Shehata et al., 2010).

BTK Deficiency (X-linked agammaglobulinemia or Bruton's agammaglobulinemia)

Pathogenesis: This deficiency, identified in 1952 by Bruton as agammaglobulinemia, was the first acknowledged PID (Bruton, 1952). BTK deficiency is distinguished by a severe reduction in B-cells and all Ig isotypes. The pathogenesis is a defect in the Bruton tyrosine kinase (BTK) gene, which is crucial to B-cell development. The BTK protein is involved in

B-cell receptor signaling, leading to immature B-cells (pre-B-cells) that do not produce antibodies (Brunner et al., 2005). BTK has also recently been confirmed as a modulator of inflammation by inhibiting TLR-induced (Toll-like receptor) cytokine production in dendritic cells and monocytes (Marron et al., 2012, Chinen et al., 2013). Clinical symptoms usually appear after the first 6 months of life when maternal antibodies are depleted. Sinopulmonary infections, conjunctivitis, diarrhea, and dermatologic infections are commonly seen, though the most frequent disease observed is recurrent otitis media (Conley & Howard, 1993).

Treatment: Regular gammaglobulin treatment (lifetime of patient) combined with prophylactic antibiotics is the recommended therapy, while stem cell gene therapy may be an option in the future for a cure.

Oral manifestations: Oral and periodontal problems include ulcerations, candidiasis, and gingivitis (Porter & Scully, 1994, Meighani et al., 2011), with recurrent aphthae being the most frequent manifestation (Meighani et al., 2011). Robertson et al, over a 2-year period of therapy and follow-up, did not see acute gingival or mucosal lesions in their study population (Robertson et al., 1980).

Common Variable Immunodeficiency Disorders (CVID)

Pathogenesis: CVID is a diverse and complex group of disorders of varying clinical makeup, typified by low IgG plus low IgA and/or IgM. B-cell numbers are usually decreased (approximately 80% of time), but can be normal. The exact molecular pathogenesis for most cases is unknown, although singular genetic defects have been identified for a small subgroup of patients (Fuleihan & Etzioni, 2012, Salzer et al., 2012). Clinically, phenotypic expression is mainly of two types. Recurrent infections are typical in one type, and the other type is characterized also by lymphoproliferative disease, interstitial pulmonary disease (may resemble sarcoidosis) and bronchiectasis, splenomegaly, granulomatous disease, gastrointestinal inflammatory disease, autoimmune cytopenias, and increased risk of malignancies (McCusker & Warrington, 2011, Salzer et al., 2012, Cunningham-Rundles, 2012, Resnick et al., 2012). Although young children and older adults are at times diagnosed with CVID, this disorder is usually detected in adults between the ages of 20 and 40 (Cunningham-Rundles, 2012). Cunningham-Rundles and Bodian in a study of 248 CVID patients followed for 1–25 years found their age range at diagnosis to be 3–79 years (Cunningham-Rundles & Bodian, 1999). CVID is also one of the ever increasing PID conditions where autoimmunity is seen in a high percentage of patients (Bacchetta & Notarangelo, 2013).

Treatment: Basic treatment for CVID is still Ig replacement, although future identification of disease-causing genes will hopefully lead to optimal curative therapy (Morio, 2012). Mortality is 11 times higher for patients with noninfectious complications (Resnick et al., 2012), and the main cause of death in adult-onset CVID is lymphoma and other cancers (Quinti et al., 2012).

Oral manifestations: Periodontal manifestations seen in CVID patients include a high incidence of aphthae (Meighani et al., 2011), herpetic ulcerations (Chavez-Garcia et al., 2015), lichenoid-like lesions (Engstrom et al., 1992), increased susceptibility for odontogenic infection (Porter & Scully, 1993b), and generalized necrotizing periodontitis (Dalla Torre et al., 2012).

CD40L/CD40 Deficiencies (Hyper-IgM Syndrome)

Pathogenesis: Serum IgG and IgA are both decreased in CD40 Deficiencies, with IgM being near normal or elevated. The XL CD40 Ligand (CD40L) Deficiencies are caused by mutations in the CD40L gene, while the AR forms (CD40 Deficiency) are caused by defects in CD40 transmembrane proteins which belong to the tumor necrosis factor (TNF) family (Qamar & Fuleihan, 2013, Mavroudi & Papadaki, 2011). The CD40L protein must ligate with its receptor protein, CD40, to initiate signaling pathways necessary for B-cell proliferation and differentiation (Bishop et al., 2007). The most common clinical traits seen are respiratory infections, chronic diarrhea, otitis, warts, mucosal ulcers (oral and rectal), and autoimmunity (Levy et al., 1997, Notarangelo et al., 1992, Chang et al., 1998). Chronic neutropenia is often observed (Notarangelo et al., 1992), and up to 70% of patients with XL type can be neutropenic (Mavroudi & Papadaki, 2011).

Treatment: The only treatment for a chance at a cure of XL CD40 disease is stem cell transplantation (Tsai et al., 2012), although it has recently been shown that immune function can be improved with long-term weekly administration of recombinant CD40L (Jain et al., 2011). Ig replacement therapy continues to be viable treatment for the less severe form of Hyper-IgM (Silva & Da Costa, 2010, Qamar & Fuleihan, 2013).

Oral manifestations: Increased susceptibility to infection and recurrent mucosal ulcerations are common oral findings.

Selective IgA Deficiency

Pathogenesis: Selective IgA Deficiency (IgAD) is the most common PID with a reported incidence as high as 1 in 300 persons (Nikfarjam et al., 2004, Boyle & Buckley, 2007). IgA is decreased or absent, and the genetic source of the defect is still unidentified (Yel, 2010, Fuleihan & Etzioni, 2012). However, MHC gene halotypes have been associated with increased predisposition to this disorder (Wang & Hammarstrom, 2012, Yel, 2010). The literature suggests that most patients with IgAD are asymptomatic, though recent findings suggest otherwise (Dincer & Dunitz, 2012, Ocampo & Peters, 2013, Jorgensen et al., 2013). A significant percentage of patients present with sinopulmonary infections, allergic disorders, and autoimmune disease (Binek & Jarosz-Chobot, 2012). Jorgensen et al studied 32 adults with IgAD versus 63 age/gender-matched controls and found 25% of test subjects had at least 1 or more bouts of pneumonia in the preceding two years of the study as opposed to only 1.6% of controls (Jorgensen et al., 2013). They also discovered a high incidence of autoimmunity (Jorgensen et al., 2013), and it has been suggested by Wang and Hammarström that IgAD in itself is an autoimmune disease (Wang & Hammarstrom, 2012). A small amount of IgAD cases will progress to CVID (Al-Herz et al., 2011, Aghamohammadi et al., 2008).

Treatment: Treatment is focused on specific infections that may arise from IgAD, and many patients may need long-term prophylactic chemotherapy for recurrent illness. Ig treatment is not indicated for Selective IgAD (Bonilla et al., 2005).

Oral manifestations: Periodontal manifestations observed have been candidiasis, stomatitis, recurrent aphthae, and herpes labialis (Porter & Scully, 1993a, Jorgensen et al., 2010, Fernandes et al., 2012), although several papers have failed to discover any oral problems in this group (Robertson et al., 1980, Nikfarjam et al., 2004, Engstrom et al., 1992). In the study by Jorgensen et al 2010 on oral health status in IgAD patients, it was detected that IgAD predisposed to oral mucosal disease but did not significantly affect periodontal or dental health (Jorgensen et al., 2010). Fernandes et al and Dahlén et al both found similar results in that Ig-deficient individuals did not exhibit increased susceptibility to caries or periodontal disease (Fernandes et al., 2012, Dahlen et al., 1993). Tar et al investigating IgAD in children discovered an increased risk of dental caries, but not periodontal disease versus their normal control population (Tar et al., 2008).

Transient Hypogammaglobulinemia of Infancy (THI)

Pathogenesis: THI is distinguished by low levels of IgG that persist beyond 6 months of age. IgA is also decreased in these patients, and the pathogenesis of this defect is unknown (Al-Herz et al., 2011). THI is one of the most common pediatric immunodeficiencies (Stiehm, 2007, Grumach et al., 1997), and is probably underdiagnosed. IgG, unlike other Ig, will cross the placenta and give newborns protection through the first few months of life. Infants will usually begin to produce their own antibodies at 3–6 months, but this is delayed up to 3 years of age in most patients with THI (Karaca et al., 2010). A small percentage of this group will display persistent low Ig production, even pass the age of 6 (Kilic et al., 2000). Moschese et al observed in 77 THI patients that most spontaneously recovered within 24 months of age, while a smaller group of the population demonstrated continued decreased IgG (Moschese et al., 2008). Although THI is generally considered to be a non-life threatening condition, studies have revealed this patient population is prone to recurrent infections (ear, sinus, respiratory), allergies/asthma, and autoimmune disease (Keles et al., 2010, Qian et al., 2009, Moschese et al., 2008). Qian et al found that otitis media was not significant in 91 THI patients, but there was an increase in upper respiratory tract infections (Qian et al., 2009).

Treatment: Medical management for these patients is usually conservative and directed at specific infections that may arise. Ig therapy is reserved for only the most severe cases, and the prognosis for most is excellent (Stiehm, 2008).

Oral manifestations: Oral candidiasis has been reported in this group infrequently (Stiehm, 2008).

Isolated IgG Subclass Deficiency (Selective IgG Deficiency)

Pathogenesis: IgG Deficiency (IgGD) is a decrease in one or more of the four IgG subclasses, varying only minimally in composition but each having very distinctive function(s) (Sigal, 2012). The exact genetic cause of IgGD has not been defined. Many

IgGD patients can be asymptomatic, but a high incidence of sinusitis, bronchitis, pneumonia, asthma, and other respiratory tract complications are frequently seen (Abrahamian et al., 2010, Oxelius et al., 1986, Olinder-Nielsen et al., 2007).

Treatment: Ig replacement therapy is effective (Abrahamian et al., 2010), and Ig prophylaxis has been shown to produce a near 60% reduction in recurrent respiratory tract infections in patients from most IgGD subclasses (Olinder-Nielsen et al., 2007).

Oral manifestations: Periodontal disease and caries activity is not increased in this group (Dahlen et al., 1993), but recurrent parotitis and oral viral ulcerations (Epstein-Barr) have been reported in IgG3 deficiency indicating a higher susceptibility to viral infections in a minority subgroup of these patients (Mitsui et al., 2003, Marsman & Sukhai, 1999).

Thymoma with Immunodeficiency (Good Syndrome)

Pathogenesis: Good Syndrome is a rare adult-onset PID which is characterized by decreased isotype(s) of serum Ig and pro-B cells, and is associated with thymic tumors. Recurrent opportunistic infections, especially sinopulmonary infections, and autoimmune conditions commonly arise in Good's patients (Arnold et al., 2015).

Treatment: Immunoglobulin therapy is usually an essential element of treatment.

Oral manifestations: Skin and oral lichen planus, as well as oral lichenoid-like lesions also frequently develop (Maehara et al., 2015, Arnold et al., 2015).

4. Diseases of Immune Dysregulation—This group of PIDs is characterized by difficulties in regulating immunity, rather than the inherent activity of parts of the immune system.

Chediak-Higashi Syndrome (CHS)

Pathogenesis: CHS is a rare AR disorder wherein the genetic defect is mutations throughout lysosomal trafficking (LYST) genes (CHS1/LYST gene), a family of proteins involved in vesicle fusion/fission (Kaplan et al., 2008). CHS1/LYST genes assemble lysosomal trafficking regulator proteins, which are responsible for the transportation of foreign substances (bacteria, etc) into cellular lysosomes. The result is large nonfunctional lysosomes with impaired degranulation capability that do not kill bacteria. NK cell and cytotoxic lymphocyte (CTL) activities are decreased (Al-Herz et al., 2011). Disease characteristics of CHS include partial albinism, hepatosplenomegaly, neutropenia, severe recurrent bacterial infections, platelet abnormalities, lymphoma-like disease, and neurologic problems (Ward et al., 2002, Rezaei et al., 2009, Wolf et al., 2006, Introne et al., 1999). A majority of patients are likely to experience an “accelerated phase” (hemophagocytic syndrome) of the disease, in which there is a lymphoproliferative surge (uncontrolled proliferation of T-cells) into major organ systems that resembles lymphoma. Much of the morbidity and mortality associated with CHS occurs during this phase. Certain proteins required for lytic granule discharge are also necessary for melanocyte function, which leads to hypopigmentation and albinism (Menasche et al., 2005).

Treatment: Long-term survival of over 60% has been reported with HCT therapy, even if treated during an active state of hemophagocytic syndrome (Eapen et al., 2007, Sparber-Sauer et al., 2009).

Oral manifestations: Periodontal and oral manifestations described are recurrent ulcers, candidiasis, and early-onset aggressive periodontitis (Delcourt-Debruyne et al., 2000, Shibutani et al., 2000, Tempel et al., 1972, Khocht et al., 2010, Rezaei et al., 2005, Hamilton & Giansanti, 1974, Bailleul-Forestier et al., 2008, Deas et al., 2003). Most of the literature reveals progressive and unsuccessful treatment of periodontal conditions due to impaired immune response, although Bailleul-Forestier et al reported a case of a 12 year-old female who underwent initial periodontal therapy and was successfully maintained over 9 years (Bailleul-Forestier et al., 2008).

APECED (APS-1) (Autoimmune PolyEndocrinopathy with Candidiasis and Ectodermal Dystrophy)

Pathogenesis: APECED, or APS-1 (Autoimmune Polyendocrinopathy Syndrome Type 1), is a rare AR disease caused by mutations in the autoimmune regulator (AIRE) gene, which encodes a transcription regulator protein (AIRE) from the thymic medulla. AIRE is critical for creating central self-tolerance by removing autoreactive T-cells from the thymus (Zumer et al., 2013). Also known as Whitaker's Syndrome, diagnosis was typically made when two out of three major criteria of Whitaker's Triad (chronic mucocutaneous candidiasis or CMC, autoimmune hypoparathyroidism, adrenocortical insufficiency) were present (Proust-Lemoine et al., 2012). However, many other autoimmune nonendocrine conditions may affect APECED patients, to include gastrointestinal (autoimmune hepatitis, atrophic gastritis, infections, malabsorption, pernicious anemia), cutaneous (alopecia, vitiligo), and/or ophthalmological (keratitis) disturbances (Proust-Lemoine et al., 2012, Millar & Carson, 2012, Kluger et al., 2013, Betterle et al., 1998). CMC is usually the first and most frequently seen sign/symptom, and generally occurs during early childhood (Betterle et al., 1998, Lopez-Jornet et al., 2005).

Treatment: Treatment is directed toward specific deficiencies, combined with immunosuppressive or immunomodulating therapies.

Oral manifestations: Oral findings commonly seen are chronic candidiasis and enamel hypoplasia (Myllarniemi & Perheentupa, 1978, Ahonen et al., 1990, Lopez-Jornet et al., 2005, Walls & Soames, 1993, Porter et al., 1995). In Ahonen et al's study, the initial clinical manifestation seen 60% of the time was oral candidiasis (Ahonen et al., 1990). Myllärniemi et al observed oral CMC in 27 of 28 patients and enamel hypoplasia in 23 of 28 patients (Myllarniemi & Perheentupa, 1978).

SAMHD1 Deficiency

Pathogenesis: SAMHD1 (SAM domain and HD domain-containing protein 1) is an enzyme (triphosphohydrolase) that converts deoxyribonucleoside triphosphates (dNTP) to triphosphate and nucleoside (Kretschmer et al., 2015). This antiretroviral protein, expressed in monocytes, macrophages, and dendritic cells, blocks HIV-1 replication in myeloid cells

by inhibiting an early essential viral life cycle step (Laguette et al., 2011). A decrease in SAMHD1 leads to an imbalance of dNTP concentrations, which in turn induces DNA destruction and activates interferon-alpha (IFN- α) production in cerebrospinal fluid. Genetic mutations of SAMHD1 cause Aicardi-Goutières syndrome (AGS), a rare early-onset inflammatory disease marked by encephalopathy, cerebral calcifications and cerebral atrophy, leukodystrophy, thrombocytopenia, skin lesions from vasculitis, and arthropathy.

Treatment: Current treatment for AGS is symptomatic.

Oral manifestations: Significant oral ulcerations can occur in these patients.

5. Congenital Defects of Phagocyte Number, Function, or Both

(1) Defects of neutrophil differentiation

Severe Congenital Neutropenia (SCN)

Pathogenesis: SCN includes a heterogeneous group of diseases distinguished by a shortage of neutrophils. The pathogenetic defect for most cases (SCN1) is an AD mutation in the elastase-neutrophil expressed (ELANE) gene, which is responsible for the manufacture of neutrophil elastase (Xia et al., 2009, Horwitz et al., 2013). The majority of AR-associated SCN (SCN3 or Kostmann Disease) is caused by a defect in the HCLS1 or HS-1 associated protein X-1 (HAX1) gene (Boztug & Klein, 2009). HAX1 is a mitochondrial protein involved in the regulation of apoptosis. A novel discovery of a G6PC3 mutation has recently been identified as the cause of SCN4 (Arostegui et al., 2009). G6PC3 deficiency (SCN4) diminishes glucose-6-phosphatase activity, resulting in abnormal glycosylation and increased apoptosis of neutrophils (Al-Herz et al., 2011). Clinical features associated with SCN are severe infection (bacterial, fungal), predisposition to malignancy (leukemia), in addition to cardiac and urogenital malformations in SCN4 patients (Connelly et al., 2012, Boztug & Klein, 2011).

Treatment: Treatment of choice for SCN is recombinant granulocyte-colony stimulating factor (G-CSF), although HCT is the only option for a cure (Sokolic, 2013). Patients with a poor response to high dose G-CSF are at greatest risk for severe infection (sepsis) and/or malignancy, and mortality in the future will expectantly decline as HCT therapy advances (Connelly et al., 2012).

Oral manifestations: SCN patients are prone to oral ulcerations, abscesses, oropharyngeal candidiasis, desquamative gingivitis, and severe periodontitis (Ye et al., 2011, Dale, 1993, Rezaei et al., 2007, Tozum et al., 2003, Goultschin et al., 2000, Hakki et al., 2005, Hasturk et al., 1998, Defraia & Marinelli, 2001).

Cyclic Neutropenia (CyN)

Pathogenesis: CyN, another major type of inherited neutropenia, is characterized by severe fluctuating neutropenia every 21 days (Dale & Welte, 2011). Like SCN, it is an AD defect in ELANE usually from single base substitutions, as opposed to the chain-terminating mutations seen in SCN (Horwitz et al., 2007). During the period of low neutrophil count, patients are susceptible to bacterial and fungal infections, fever, bacteremia, and septic shock

(Dale & Welte, 2011). Although significant, the risk of severe infection in CyN patients is not as great as in SCN individuals, and CyN is not associated with a risk for MDS (myelodysplasia) or AML (acute myelogenous leukemia) (Dale et al., 2003, Dale, 1993).

Treatment: Effective treatment is generally SC G-CSF every day or on alternate days, and symptoms usually improve with age (Dale & Welte, 2011).

Oral manifestations: Periodic aphthous stomatitis and severe periodontal disease are known manifestations of CyN (Chen et al., 2013, Lu & Meng, 2012, Hart et al., 1994, Pernu et al., 1996).

Glycogen Storage Disease Type 1b (GSD1)

Pathogenesis: GSD1, the most common GSD, is an AR mutation of the glucose-6-phosphatase (G6Pase) transporter gene (G6PT1). G6PT1 is responsible for translocating glucose-6-phosphate (G6P) from cellular cytoplasm into the endoplasmic reticulum (ER) lumen, where G6Pase (in the ER) hydrolyzes G6P to glucose and phosphate (Lee et al., 2012). The end result from the diminished activity of the G6Pase System is a lack of glucose production from glycogen and reduced glucose homeostasis (Chou et al., 2013). Chronic hypoglycemia leads to accumulation of lipids and glycogen in hepatocytes and kidneys. Hyperlipidemia, hepatic stenosis (hepatomegaly), and renal dysfunction can result in liver tumors (adenomas with capacity for malignancy) and end-stage nephropathy (Rajas et al., 2013). GSD patients also exhibit growth retardation (“doll-like” fat cheeks, thin extremities, short and bulging physique), lactic acidosis, hyperuricemia, neutropenia, neutrophil and monocyte dysfunction (decreased chemotaxis and superoxide production), and bleeding tendencies from diminished platelet function (Bali et al., 1993, Chou, 2001). The neutropenia in GSD is not caused by a lack of neutrophil maturation, but rather an increase in apoptosis and an efflux of PMNs from blood to inflamed tissues (Visser et al., 2012). GSD1b is the only GSD type where neutropenia and/or neutrophil dysfunction occurs (Kannourakis, 2002).

Treatment: With dietary management and treatment targeted toward specific organ systems involved, the prognosis for GSD patients can be reasonably good. They are capable of having an almost normal life span (Froissart et al., 2011).

Oral manifestations: Periodontal and oral manifestations include increased propensity for bacterial infections, periodontal disease to include overgrown gingiva, multiple tongue and mucosal ulcers, oral bleeding, giant cell granulomatous epulis, dental caries, and hypomineralized enamel (Bartoli et al., 2006, Mortellaro et al., 2005, Salapata et al., 1995).

(2) Defects of motility

Leukocyte Adhesion Deficiency Type 1 (LAD1)

Pathogenesis: LAD syndromes are rare AR disorders that transpire as a result of defective recruitment (leukocyte trafficking) of leukocytes from the intravascular compartment (Notarangelo & Badolato, 2009, Schmidt et al., 2013). This recruitment of leukocytes, termed the “leukocyte adhesion cascade” (LAC), traditionally comprised the three steps of

rolling, activation, and firm adhesion. The LAC stages today have been supplemented to include capture (tethering), rolling, slow rolling, arrest, adhesion strengthening and spreading, intravascular crawling, plus paracellular and transcellular transmigration (Ley et al., 2007). Previous terminology for LAD was Lazy Leukocyte Syndrome, which generally referred to diseases with leukocyte chemotaxis defects. These diseases are now classified according to their specific pathogenetic cause. LAD1, the most common type of LAD, is a defect in the beta-2 integrin gene (INTGB2) subunit (also called CD18) of the leukocyte cell adhesion protein (Hanna & Etzioni, 2012).

Treatment: Curative therapy is HCT (van de Vijver et al., 2013), although the INTGB2 (CD18) gene has been replicated. Bauer et al recently published results on canine LAD (CLAD) successfully treated with foamy viral (FV) vector-mediated gene therapy with 4–7 years follow-up (Bauer et al., 2013). Conclusions reached hopefully will lead to gene therapy clinical trials soon.

Oral manifestations: Clinical findings, to include periodontal, are recurrent infections without pus formation, delayed umbilical cord separation, leukocytosis, skin ulcers, and severe aggressive periodontitis that may affect primary and permanent dentition (Notarangelo & Badolato, 2009, Al-Herz et al., 2011, Nagendran et al., 2012, Majorana et al., 1999, Yashoda-Devi et al., 2011, Cox & Weathers, 2008, Meyle, 1994, Dababneh et al., 2008).

Papillon-Lefèvre Syndrome (PLS)

Pathogenesis: PLS, a very rare AR disorder discovered in 1924, is characterized by palmoplantar hyperkeratosis (PPK) and severe periodontitis (Dalgic et al., 2011, Van Dyke et al., 1984). Haim-Munk syndrome (HMS) is a phenotypic variant of PLS (Sulak et al., 2015). The presence of early aggressive periodontal disease is what distinguishes PLS and HMS from more common forms of PPK (Hart et al., 1997). The genetic mutation in PLS is within cathepsin C (CTSC), an enzyme which coordinates activation of serine proteases necessary for immune cell function. This results in a chemotactic defect in neutrophils and monocytes-macrophages.

Treatment: Treatment for PLS is to reduce symptoms and/or complications. Life expectancy can be near normal.

Oral manifestations: Severe destructive periodontitis can lead to early loss of primary and permanent teeth, however various reports demonstrate that PLS patients can be successfully treated and managed to include dental implants (Nickles et al., 2013, Al Farraj AlDosari, 2013, Veerabahu et al., 2011, Toygar et al., 2007). Toygar et al treated a young female with periodontal therapy, orthodontics, osseous augmentation, and implants with success, and maintained her oral health after 13 years of follow-up (Toygar et al., 2007). There has lately been rising concern for the increased incidence of liver, brain, and kidney abscesses seen in PLS patients (Morgan et al., 2011, Almuneef et al., 2003, Kanthimathinathan et al., 2013, Keskin-Yildirim et al., 2012). Morgan et al recently reported on chronic granulomatous infection discovered in a renal mass in a 5-year-old female with PLS (Morgan et al., 2011).

Also of interest is the apparent high predisposition to malignant melanoma in Japanese PLS patients, a population with an elevated occurrence of hereditary PPK (Nakajima et al., 2008).

(3) Defects of respiratory burst

Chronic Granulomatous Disease (CGD)

Pathogenesis: CGD, the most common disorder of defective phagocytosis, is an ID syndrome associated with an inability of neutrophils and monocytes to effectively kill microbes (bacteria, fungi) once ingested (Roos et al., 1996). The failure to kill pathogens is due to a lack of superoxide production, consequently the intracellular microorganisms endure and initiate chronic granulomatous inflammation. X-linked CGS, the most common type of CGD, is caused by a defect in the cytochrome b β (CYBB) gene which encodes electron transport protein gp91phox (Andrews & Sullivan, 2003). CGD patients are susceptible to recurrent bacterial and fungal infections, especially catalase-positive organisms. Microbes that contain catalase will breakdown H_2O_2 , leaving host cells no free oxygen radicals to fight off infection. Fungal infections, especially pulmonary, are the major cause of death, and the mortality from fungal infection is 40% (Henriet et al., 2013, Armstrong-James & Harrison, 2012). CGD has the highest incidence of invasive fungal infection of all the ID disorders (Falcone & Holland, 2012).

Treatment: Depending on the severity of disease, treatment is usually directed toward antibiotic management of infections, HCT, and/or immunotherapy with interferon gamma (IFN- γ) administration, adoptive T-cell treatment and gene therapy (Armstrong-James & Harrison, 2012, Stein et al., 2013, Cole et al., 2013). Cole et al determined that CGD patients who were treated with HCT had better survival and less incidence of infections than those managed with antibiotic therapy alone (Cole et al., 2013). CGD, being a monogenic mutation affecting the hematopoietic system, should be responsive to future gene therapy (Stein et al., 2013).

Oral manifestations: Periodontal lesions observed are ulcerations (mucosal and keratinized tissue), gingivitis, and periodontitis (Deas et al., 2003, Cohen et al., 1985, Wolf & Ebel, 1978). The correlation with gingivitis is stronger in X-linked CGD, and with periodontitis the association is higher in the AR forms of the disease (Chien & Hart, 2013).

6. Defects in Innate Immunity—These uncommon disorders have defects in the innate system, a defense mechanism without memory that occurs promptly and relies on proteins called pattern recognition receptors (PRRs) to identify pathogens. This is in contrast to the adaptive system of lymphocytes, which has memory and is generally more specific. Conditions of innate immune defects usually are associated with dermatological problems (Al-Herz et al., 2011).

Chronic Mucocutaneous Candidiasis (CMC)

Pathogenesis: CMC can be described as repeated episodes of fungal infection (*Candida* species) of mucosal surfaces, skin, and nail beds. The transformation of immature T-cells into Th-17 cells is crucial for an effective immune response to fungi. *Candida* is detected by PRRs of innate immunity, which then normally leads to this transformation (McDonald,

2012). Th-17 cells generate IL-17 (Korn et al., 2009), and a deficiency in IL-17 is the underlying basis for CMC disease (Puel et al., 2012). The pathogenetic origins for inherited CMC are either an AR IL-17RA (interleukin 17 receptor A) mutation, an AD IL-17F alteration, or an AD STAT1 (signal transducer and activator of transcription) gain-of-function (GOF) error (Al-Herz et al., 2011). STAT1, integral to IFN- γ and IFN- α signaling, aids in the immune response to mycobacteria, fungi, viral infections, and cancer (Sampaio et al., 2012).

Treatment: Systemic antifungal agents are the mainstay of treatment, as topical preparations are not very effective in CMC patients (Jayasinghe et al., 2006).

Oral manifestations: CMC patients regularly endure oropharyngeal infection that can produce considerable pain and lead to weight loss (Huppler et al., 2012). CMC disease can also lead to multiple intracranial aneurysms and invasive disseminated mold/yeast sepsis (Soltesz et al., 2013, Sampaio et al., 2013). Multiple and long-standing candidal infection, usually since infancy, of mucosa and tongue are reported oral findings (Liu & Hua, 2007, Myhre et al., 2004).

7. Autoinflammatory Disorders—These disorders are also known as the “periodic fever syndromes,” and lead to widespread severe episodes of fever and inflammation of noninfectious origin. Most of these diseases begin in childhood, but can also occur as an adult (Muscari et al., 2012). Life-threatening damage to organ systems (amyloidosis) is observed in some cases, with renal amyloidosis being the most common form (Yao & Furst, 2008). Aphthous stomatitis has been reported as a frequent finding in many of these syndromes (Scully et al., 2008). Recurrent nonmicrobial osteomyelitis of the jaws has been described in Chronic Recurrent Multifocal Osteomyelitis and Congenital Dyserythropoietic Anemia (Majeed Syndrome) (Hofmann et al., 2012). The pathogenesis of many of these disorders is coupled to the release of IL-1 β (Savic et al., 2012).

Periodic Fever, Aphthous, Pharyngitis, Adenitis Syndrome (PFAPA)

Pathogenesis: PFAPA Syndrome (Marshall’s Syndrome), one of the most common autoinflammatory disorders (De Cunto et al., 2010) and the most common in children (Stojanov et al., 2011), is characterized by recurring high fever, aphthous stomatitis, pharyngitis, cervical adenitis, and sometimes genital ulcers (Lin et al., 2011). It is currently the only periodic fever syndrome in which the pathogenetic etiology is uncertain, however there is growing evidence that PFAPA is linked to the IL-1 pathway and IL-1 inhibition is beneficial for these patients (Stojanov et al., 2011). Kolly et al recently discovered that IL-1 β monocyte production is dysregulated in PFAPA patients (Kolly et al., 2013). PFAPA usually manifests before the age of 5 and resolves by teen years, but Padeh et al reported on 15 adults that experienced active disease attacks at 4–8 week intervals (Padeh et al., 2008).

Treatment: Successful therapy has been to give 1 to 2 doses of prednisone for episodic outbreaks, although its efficacy is not permanent (Murata et al., 2007). One study showed all symptomatic occurrences in adult patients were aborted with a 60 mg single dosage of prednisone (Padeh et al., 2008). Cimetidine plus tonsillectomy surgery has been advocated,

and Licameli et al revealed that adenotonsillectomy surgical treatment provided complete resolution of symptoms in 99 of 102 PFAPA pediatric patients (Licameli et al., 2012). Prognosis for these patients is usually good.

Oral manifestations: Periodontal and oral signs and symptoms frequently seen are aphthous-like lesions (Pinto et al., 2006), and oral health care practitioners should be aware of this syndrome as they may very well be the first ones to evaluate these patients (Femiano et al., 2008).

Familial Mediterranean Fever (FMF)

Pathogenesis: FMF is due to mutations in the MEFV (Mediterranean Fever) gene, which results in ASC-dependent (apoptosis-associated speck-like protein with a caspase recruitment domain) IL-1 activation and subsequent inflammation following serosal cavity (pericardial, pleural, peritoneal) injury (Al-Herz et al., 2011). Clinical features are sporadic recurrent fever and serositis lasting 1 to 3 days. FMF patients may develop dermatologic lesions, arthralgia, and renal amyloidosis (Grattagliano et al., 2013). Oral ulcerations are frequently encountered (Yao & Furst, 2008, Grattagliano et al., 2013).

Treatment: Goals of therapy are to prevent attacks with life-long medication and to block the development of amyloidosis. Colchicine, a drug that accumulates in neutrophils and inhibits their activity, is a safe and effective treatment for many (Cocco et al., 2010). Approximately 5 to 15% of patients don't respond to colchicine (Yao & Furst, 2008), and many are candidates for IL-1 receptor antagonist and/or IL-1 decoy receptor therapy (Grattagliano et al., 2013). A significant number of patients, even with good therapeutic compliance, may progress to end-stage renal disease (Korkmaz, 2012).

Oral manifestations: The prevalence of moderate to severe periodontitis in familial Mediterranean fever patients with amyloidosis has been reported to be significantly greater ($p < 0.01$) than in familial Mediterranean fever patients without amyloidosis (Cengiz et al., 2009).

Hyper IgD Syndrome (HIDS)

Pathogenesis: HIDS is also termed Mevalonate Kinase (MVK) Deficiency due to the mutational defect being in the MVK gene. MVK is vital for cholesterol synthesis (Sakai & Heike, 2011), yet the pathophysiology of why this deficiency leads to periodic fever has not been elucidated. HIDS patients suffer from fever for 3–7 days every 4–6 weeks, lymphadenopathy, abdominal pain, diarrhea, vomiting, arthralgia, and skin lesions (Gencpinar et al., 2012). Renal angiomyolipomas have also been diagnosed in a minority of this patient group (Bader-Meunier et al., 2011). The febrile episodes usually occur throughout life, though the frequency of attacks is highest in childhood and adolescence (Drenth & van der Meer, 2001). Elevated leukocyte, C-reactive protein, IL-1, IL-6, and TNF levels are seen in this population (Korppi et al., 2011). Most patients have their first symptomatic outbreak in the first year of life, typically after a childhood vaccination (van der Hilst & Frenkel, 2010).

Treatment: The biologic modifying drugs entanercept, a TNF α inhibitor, and anakinra, an IL-1 receptor antagonist, are the current mainstays of treatment. Bader-Maunier et al revealed that IL-1 antagonists were the most effective biological agents (Bader-Maunier et al., 2011), although Shendi et al observed severe prolonged attacks in a 10-year-old female after treatment with entanercept and anakinra (Shendi et al., 2012). Prognosis is usually good, though amyloidosis has recently been reported in four MVK deficient patients (Lane et al., 2013).

Oral manifestations: Oral ulcerations have been observed in a smaller subgroup of HIDS patients (Drenth & van der Meer, 2001, Yao & Furst, 2008, Gencpinar et al., 2012).

Cherubism

Pathogenesis: Cherubism is a rare fibro-osseous condition of the maxillofacial region where bone is resorbed and replaced by fibrous tissue, resulting in disfigurement. The genetic defect is a neomorphic (gain-of-function) mutation of the SH3BP2 protein, which leads to increased TNF- α production and NF- κ B ligand (RANKL)-induced osteoclastogenesis in myeloid cells. The disease can be self-limiting and regression often is observed post puberty.

Treatment: Plastic surgery and/or orthodontic therapy may be indicated once lesions stabilize. Recent reports have shown that calcineurin (protein phosphatase 3) inhibitors, which block SH3BP2-induced overactivation of nuclear factor of activated T-cells, may offer new medical treatments for cherubism (Kadlub et al., 2015).

Oral manifestations: Affected patients can present with bilateral jaw swelling (mandible more than maxilla), early loss of primary teeth, unbalanced eruption or failed eruption of permanent teeth, and malocclusion (Ahmed & Amin, 2014).

CANDLE (Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy) Syndrome

Pathogenesis: CANDLE, first described by Torrelo et al as Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature Syndrome (Torrelo et al., 2010), is caused by mutations in the proteasome subunit β type 8 (PSMB8) gene leading to increased IL-6 production. Reported manifestations in patients are early onset recurrent fever, skin purpura, periorbital erythema and purple eyelids, thickened lips, joint contractures, arthralgia, panniculitis with progressive lipodystrophy, CNS calcifications, and diabetes mellitus (Wang et al., 2014).

Treatment: Medical management with steroids and newer specific therapies, such as biologic modifiers, have shown very limited and inconsistent results.

Oral manifestations: Severe periodontal disease has been reported in the literature for the first time in an 11-year old patient recently (McKenna et al., 2013). Quality of life can be reduced and life expectancy is uncertain in CANDLE patients.

8. Complement (C) Deficiencies—Complement proteins that bind to pathogens and form a membrane attack complex (MAC) are crucial for our immune system to guard against microbial disease. Activation of the complement system is very precise, and C3 plays a major role in initiation of immune responses (Tichaczek-Goska, 2012). Genetic deficiencies of complement lead to increased susceptibility to infection. Patients with C3 deficiency are vulnerable to severe infections, as C3 is the central component of the complement cascade (Daha, 2010). There is growing evidence that connects complement activation and subversion of innate immunity to the pathogenesis of periodontal disease (Hajishengallis, 2010).

C3 Deficiency

Pathogenesis: Mutational defects of C3, the merging point for all complement pathways, can lead to life-threatening infections from meningococcal and pneumococcal disease, as well as other encapsulated microbial species (Ram et al., 2010). Total C3 deficiency is rare, but is the most serious of the complement deficiencies because of predisposition to recurrent and invasive infection. C3 is the major opsonin of complement system, and facilitates anaphylatoxin production, and B-cell activation with Ig production. Besides recurrent suppurative infection, C3 patients are also prone to glomerulonephritis from excess immune complex buildup, SLE-like disease (systemic lupus erythematosus), and AMD (age-related macular degeneration) (Zipfel et al., 2010, Java et al., 2013). Mutations in Factors I and H (regulatory proteins) can result in secondary C3 deficiencies (Jayasinghe et al., 2006). Fu et al recently demonstrated that C3 plays a valuable role in Alzheimer's Disease prevention, in that C3 is involved in clearance of A β (fibrillar amyloid- β) by glial cells (microglia) of the CNS (Fu et al., 2012).

Treatment: Antibiotic prophylaxis is appropriate when indicated for recurrent sepsis. Vaccinations are not contraindicated and should be kept up-to-date (Tedesco, 2008). Gene therapy should be a realistic future expectation.

Oral manifestations: There are no reports in the literature of specific intraoral complications from C3 deficiency. Treatment is supportive and usually geared toward control of infection.

9. Phenocopies of PID—This is a new category of PID added to the 2014 updated version of IUIS classifications. This new group was added because certain conditions present as inherited immunodeficiencies, but are the result of acquired changes instead of hereditary (germline) mutations. Diseases in this category are associated with either somatic mutations of certain immune cells or with autoantibodies against specific cytokines. The number of conditions in this grouping will likely increase in the near future.

Chronic Mucocutaneous Candidiasis (isolated or with APECED): In this newly classified disorder manifested as CMC, the genetic defect is autoantibodies to IL-17 and/or IL-22 (Al-Herz et al., 2014). Pathological features associated with CMC are endocrinopathy and persistent fungal infections. Circulating T-cell numbers are normal.

SECONDARY IMMUNODEFICIENCIES (Acquired)

As opposed to PIDs in which the individual has an inherited defect in his/her immune system, patients with SIDs are born with normal immunity but some condition or external factor results in an immunocompromised state. The most prominent SID in the world is Acquired Immunodeficiency Syndrome (AIDS), yet the most frequent cause of ID of any kind is severe malnutrition (Chinen & Shearer, 2008). Malnutrition retards immune responses which can increase susceptibility to infection (Gupta et al., 2009). Other diseases or conditions that may give rise to SID are immunosuppressive treatment (chemotherapy, transplantation), malignancies (leukemia, myeloma, lymphoma), asplenicism, uncontrolled diabetes, autoimmune disorders, toxic exposures (drugs, alcohol, tobacco), stress, aging, and other genetic illnesses (Down's Syndrome, Hypophosphatasia, Acatalasia). This list can be extensive, and we will only cover the major reasons for SID in this manuscript.

1. Acquired Immunodeficiency Syndrome (AIDS)

Pathogenesis: The most well-known SID is AIDS, most cases of which are caused by the lentivirus (retrovirus) HIV-1. The origin of HIV came from cross-species infection with Simian Immunodeficiency Virus (SIV), which resides naturally in non-human primates. Transmission to humans involving SIVcpz (SIV in chimpanzees) from chimps in southeastern Cameroon, Africa, triggered HIV-1 Group M, the chief cause of the AIDS pandemic (Sharp & Hahn, 2011). There are over 30 million cases worldwide and between 1.5 to 2 million deaths per year in persons living with HIV (PLHIV), the majority occurring in sub-Saharan Africa (Chang et al., 2013, Johnson, 2010). Mucosal dendritic cells (DCs), APCs that link the innate and adaptive immune responses, are among the first cells to encounter HIV-1, and are involved in transfer of HIV-1 to CD4+ T-cells in infectious synapses that promote HIV expansion in the host (Wu & KewalRamani, 2006). Other monocyte-lineage cells, monocytes and macrophages (also APCs), are also reservoirs of HIV-1, and contribute to HIV infection and transmission (Wu, 2011).

Treatment: Despite the advancement of HAART and its role in disruption of viral load, rebound from these latent sources (monocytes, CD4 T-cells) is a major hurdle to cross in eliminating HIV (Abbas & Herbein, 2012). Therapeutic vaccines aimed at APC responses are advocated, and indeed, the best results from vaccine trials so far have been DC-based vaccines (Garcia et al., 2013). This reinforces the crucial function that DCs have in HIV dissemination. HAART has significantly altered HIV infection and reduced AIDS-related morbidity and mortality. In the pre-HAART era, AIDS-associated malignancies (Kaposi's sarcoma, lymphoma), as well as pneumocystis pneumonia, were a major cause of death (Stewart et al., 2012). Conversely, the main causes of death in the post-HAART period have been liver disease, cardiovascular disease, lung disease, renal disease, and non-AIDS-related cancer (Palella et al., 2006). Drug overdose, suicide, and violence have also significantly contributed to the mortality rate in the post-HAART era (Krentz et al., 2005). HAART has also changed the frequency of intraoral lesions observed. Less oral hairy leukoplakia, Kaposi's, and necrotizing periodontitis is seen, while human papilloma virus (HPV) and caries seem to be on the rise (Davoodi et al., 2010).

Oral manifestations: The prevalence and progression of periodontal disease has been modified with the advent of HAART (Mataftsi et al., 2011), especially the reduced incidence of necrotizing periodontal disease reported (Phiri et al., 2010). While it seems that there have been significant reductions in HIV-related oral lesions, oral manifestations of the syndrome are still commonplace despite HAART (Tami-Maury et al., 2011a). Some reports suggest the incidence of oral candidiasis is decreasing, however others question this conclusion (Patton et al., 2013). Tami-Maury et al in a study of 744 patients on HAART found 36% had one or more oral lesions, and the most frequent finding 75% of the time was oropharyngeal candidiasis (Tami-Maury et al., 2011b). Berberi and Noujeim reported recently that the most common oral lesion (76%) out of 50 patients was pseudomembranous candidiasis (Berberi & Noujeim, 2015). Recent studies suggest an increase in oral HPV infection in AIDS patients despite compliance with HAART (Hagensee et al., 2004). Certain subtypes of HPV (16 and 18) are a major cause of oropharyngeal cancer (OPC) (Cogliano et al., 2005). The current increased incidence of OPC witnessed in the U.S. is a direct reflection on the proliferation of HPV infection in this population (Chaturvedi et al., 2011). HPV vaccination shows promise, and Herrero et al recently showed that a bivalent HPV vaccine gave protection against oral HPV infection, confirming the potential for preventing HPV-associated OPC (Herrero et al., 2013). With HIV infection now being somewhat medically controllable, periodontal and dental healthcare personnel must be informed and attentive to the needs of this group of patients.

2. Malnutrition

Pathogenesis: Undernourishment is the most serious form of malnutrition in the world, and for many populations, accounts for over half of their total annual mortality. It is a huge public health issue and has life-long impacts if happens during early childhood at key stages in growth and development (Victora et al., 2010). It has been estimated that more than a third of deaths in children globally are directly attributable to malnutrition (Black et al., 2008). Malnutrition is the single most significant predisposing factor to disease in humans on the planet, and undernutrition is central as a primary cause of child deaths associated with infectious disease (Black et al., 2003). Indeed, one has to wonder why a problem with such sweeping consequences to the human populace is relatively neglected, as compared to a disease like AIDS which attracts much more attention and resources (Shiffman, 2009). There are many detrimental consequences to the body if micronutrient (vitamins, minerals) homeostasis is not maintained. Vitamin D is expressed by virtually all cells of the immune system. Vitamin D deficiency is normally associated with bone metabolism disease (Panayiotopoulos et al., 2013), but its effects are much more variable (Bell, 2011a). Manifestations linked to vitamin D deficiency are autoimmune diseases, allergies, asthma, certain cancers, diabetes, cardiovascular events, Alzheimer's, schizophrenia, depression, and musculoskeletal weakness (Bell, 2011b, Bell, 2011c). Vitamin A deficiency is the major cause of blindness (xerophthalmia) in the world in children (McLaren, 1999), and Vitamin K is essential for blood coagulation. Anemia, most frequently caused by iron and/or vitamin B₁₂ deficiency (Fernandez-Banares et al., 2009), can lead to atrophic glossitis, stomatitis, and mucosal ulceration (Sweeney et al., 1994, Lehman et al., 2006, Lu & Wu, 2004). Scurvy (vitamin C deficiency), still a prevalent disease in many patient cohorts, is characterized by

gingival bleeding and swelling, joint pain and myalgias, pedal edema, and fatigue (Olmedo et al., 2006). Vitamin C deficiency can be associated with not only undernutrition, but also psychological problems (Bacci et al., 2010), usually an issue of concern in underdeveloped countries.

Treatment: Access to adequate nutritional intake is a basic right for all humanity. It must be afforded to all and in a safe manner, especially those individuals who are starved in developing countries and are susceptible to Refeeding Syndrome (sudden reintroduction of nutrition to patients who are starved and/or malnourished, can cause life-threatening electrolyte disorders) (Fernandez Lopez et al., 2009). Current economic crises in many areas of the world potentially endanger the gains achieved worldwide to feed the hungry. It is everyone's problem, not just the needy.

Oral manifestations: Malnourishment affects the function of all organ systems (Saunders & Smith, 2010), as well as the periodontium, mucosal tissues, dentition, salivary glands and perioral skin (Thomas & Mirowski, 2010). Caries and periodontitis are directly affected by diet and nutrition (Touger-Decker et al., 2003).

CONCLUSIONS

In conclusion, the periodontium is a highly vascular tissue, protected by a network of innate and adaptive immune cells factors whose predominant function is to prevent the penetration of microbes further into the host integument. Based on an extensive review of the literature, bacterial plaque related periodontal diseases seem particularly sensitive to primary deficiencies in the innate immune system, most involving deficient number and function of phagocytes. These include neutrophils and monocytes. Neutrophils kill bacteria directly using their intracellular granules but phagocytosis of encapsulated bacterial requires complement opsonization. Monocytes are precursors to antigen presenting cells, macrophages and dendritic cells, which must capture and process antigens for initiation of the adaptive immune response involving B- and T cells. Most non-bacterial related oral or periodontal infections are particularly sensitive to deficiencies in the adaptive immune response involving deficient antigen presenting molecules on APCs, and the number of T and B cells, or the antibody production by B cells/plasma cells. These include candidiasis, herpes simplex, oral aphthae and stomatitis. The impact of all of these deficiencies, however, pale in comparison to the influence of malnutrition in overall oral and general health globally. New technology, such as genetic sequencing, has led to greater knowledge and understanding of the immunodeficiency diseases. Clinical and laboratory screening for any suspected immunodeficient condition must be expedited in order to shorten the interval from signs/symptoms to diagnosis. Only then can we have a significant impact on morbidity, mortality, and quality of life for these patients.

Acknowledgments

Source of Support: This work was supported by U.S. Public Health Service grants from the U.S. National Institutes of Health/National Institute of Dental and Craniofacial Research DE014328 and DE020916 to C.W.C.

References

- Abbas W, Herbein G. Molecular Understanding of HIV-1 Latency. *Adv Virol.* 2012; 2012:574967. [PubMed: 22548060]
- Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. *Clin Exp Immunol.* 2010; 159:344–50. [PubMed: 20015274]
- Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, Hammarstrom L. Progression of selective IgA deficiency to common variable immunodeficiency. *Int Arch Allergy Immunol.* 2008; 147:87–92. [PubMed: 18520152]
- Ahmed B, Amin M. Postpubertal cherubism with Noonan syndrome. *J Coll Physicians Surg Pak.* 2014; 24(Suppl 1):S39–40. [PubMed: 24718001]
- Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med.* 1990; 322:1829–36. [PubMed: 2348835]
- Al Farraj AlDosari A. Oral rehabilitation of a case of Papillon-Lefevre syndrome with dental implants. *Saudi Med J.* 2013; 34:424–7. [PubMed: 23552598]
- Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, Etzioni A, Fischer A, Franco JL, Geha RS, Hammarstrom L, Nonoyama S, Notarangelo LD, Ochs HD, Puck JM, Roifman CM, Seger R, Tang ML. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol.* 2011; 2:54. [PubMed: 22566844]
- Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Franco JL, Gaspar HB, Holland SM, Klein C, Nonoyama S, Ochs HD, Oksenhendler E, Picard C, Puck JM, Sullivan K, Tang ML. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol.* 2014; 5:162. [PubMed: 24795713]
- Aldous JA, Olson GJ, Parkin MJ. Dental observations of hyper IgE disorder. *J Clin Pediatr Dent.* 2007; 32:69–72. [PubMed: 18274475]
- Allenspach, E., Rawlings, D., Scharenberg, A. X-Linked Severe Combined Immunodeficiency. In: Pagon, RA, Adam, MP, Bird, TD, Dolan, CR, Fong, CT., Stephens, K., editors. *GeneReviews*. Seattle (WA): 1993.
- Almuneef M, Al Khenazian S, Al Ajaji S, Al-Anazi A. Pyogenic liver abscess and Papillon-Lefevre syndrome: not a rare association. *Pediatrics.* 2003; 111:e85–8. [PubMed: 12509601]
- Andrews T, Sullivan KE. Infections in patients with inherited defects in phagocytic function. *Clin Microbiol Rev.* 2003; 16:597–621. [PubMed: 14557288]
- Armstrong-James D, Harrison TS. Immunotherapy for fungal infections. *Curr Opin Microbiol.* 2012; 15:434–9. [PubMed: 22884572]
- Arnold SJ, Hodgson T, Misbah SA, Patel SY, Cooper SM, Venning VA. Three difficult cases: the challenge of autoimmunity, immunodeficiency and recurrent infections in patients with Good syndrome. *Br J Dermatol.* 2015; 172:774–7. [PubMed: 25059810]
- Arostegui JJ, de Toledo JS, Pascal M, Garcia C, Yague J, Diaz de Heredia C. A novel G6PC3 homozygous 1-bp deletion as a cause of severe congenital neutropenia. *Blood.* 2009; 114:1718–9. [PubMed: 19696212]
- Atkinson JC, Harvey KE, Domingo DL, Trujillo MI, Guadagnini JP, Gollins S, Giri N, Hart TC, Alter BP. Oral and dental phenotype of dyskeratosis congenita. *Oral Dis.* 2008; 14:419–27. [PubMed: 18938267]
- Atkinson JC, O'Connell A, Aframian D. Oral manifestations of primary immunological diseases. *J Am Dent Assoc.* 2000; 131:345–56. [PubMed: 10715926]
- Bacchetta R, Notarangelo LD. Immunodeficiency with autoimmunity: beyond the paradox. *Front Immunol.* 2013; 4:77. [PubMed: 23630524]
- Bacci C, Sivoilella S, Pellegrini J, Favero L, Berengo M. A rare case of scurvy in an otherwise healthy child: diagnosis through oral signs. *Pediatr Dent.* 2010; 32:536–8. [PubMed: 21462768]

- Bader-Meunier B, Florkin B, Sibilia J, Acquaviva C, Hachulla E, Grateau G, Richer O, Farber CM, Fischbach M, Hentgen V, Jegou P, Laroche C, Neven B, Lequerre T, Mathian A, Pellier I, Toutou I, Rabier D, Prieur AM, Cuisset L, Quartier P, Sofremip and Cri. Mevalonate kinase deficiency: a survey of 50 patients. *Pediatrics*. 2011; 128:e152–9. [PubMed: 21708801]
- Bailleul-Forestier I, Monod-Broca J, Benkerrou M, Mora F, Picard B. Generalized periodontitis associated with Chediak-Higashi syndrome. *J Periodontol*. 2008; 79:1263–70. [PubMed: 18597610]
- Bali, DS., Chen, YT., Goldstein, JL. Glycogen Storage Disease Type I. In: Pagon, RA. Adam, MP. Bird, TD. Dolan, CR. Fong, CT., Stephens, K., editors. *GeneReviews*. Seattle (WA): 1993.
- Ballew BJ, Savage SA. Updates on the biology and management of dyskeratosis congenita and related telomere biology disorders. *Expert Rev Hematol*. 2013; 6:327–37. [PubMed: 23782086]
- Ballow M. Immunoglobulin therapy: methods of delivery. *J Allergy Clin Immunol*. 2008; 122:1038–9. [PubMed: 18804269]
- Bartoli A, Bossu M, Sfasciotti G, Polimeni A. Glycogen Storage Disease type Ib: a paediatric case report. *Eur J Paediatr Dent*. 2006; 7:192–8. [PubMed: 17168629]
- Bauer TR Jr, Tuschong LM, Calvo KR, Shive HR, Burkholder TH, Karlsson EK, West RR, Russell DW, Hickstein DD. Long-term follow-up of foamy viral vector-mediated gene therapy for canine leukocyte adhesion deficiency. *Mol Ther*. 2013; 21:964–72. [PubMed: 23531552]
- Bell DS. Protean manifestations of vitamin D deficiency, part 1: the epidemic of deficiency. *South Med J*. 2011a; 104:331–4. [PubMed: 21606711]
- Bell DS. Protean manifestations of vitamin D deficiency, part 2: deficiency and its association with autoimmune disease, cancer, infection, asthma, dermatopathies, insulin resistance, and type 2 diabetes. *South Med J*. 2011b; 104:335–9. [PubMed: 21606712]
- Bell DS. Protean manifestations of vitamin D deficiency, part 3: association with cardiovascular disease and disorders of the central and peripheral nervous systems. *South Med J*. 2011c; 104:340–4. [PubMed: 21606713]
- Berberi A, Noujeim Z. Epidemiology and Relationships between CD4+ Counts and Oral Lesions among 50 Patients Infected with Human Immunodeficiency Virus. *J Int Oral Health*. 2015; 7:18–21.
- Betterle C, Greggio NA, Volpato M. Clinical review 93: Autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab*. 1998; 83:1049–55. [PubMed: 9543115]
- Binek A, Jarosz-Chobot P. Selective immunoglobulin A deficiency. *Pediatr Endocrinol Diabetes Metab*. 2012; 18:76–8. [PubMed: 22781885]
- Bishop GA, Moore CR, Xie P, Stunz LL, Kraus ZJ. TRAF proteins in CD40 signaling. *Adv Exp Med Biol*. 2007; 597:131–51. [PubMed: 17633023]
- Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J, Maternal and Child Undernutrition Study G. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008; 371:243–60. [PubMed: 18207566]
- Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet*. 2003; 361:2226–34. [PubMed: 12842379]
- Blackburn MR, Thompson LF. Adenosine deaminase deficiency: unanticipated benefits from the study of a rare immunodeficiency. *J Immunol*. 2012; 188:933–5. [PubMed: 22262755]
- Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP Jr, Orange JS, Routes JM, Shearer WT, Sorensen RU, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005; 94:S1–63. [PubMed: 15945566]
- Boraz RA. Dental considerations in the treatment of Wiskott-Aldrich syndrome: report of case. *ASDC J Dent Child*. 1989; 56:225–7. [PubMed: 2656796]
- Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, Merritt RK, O'Leary LA, Wong LY, Elixson EM, Mahle WT, Campbell RM. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics*. 2003; 112:101–7. [PubMed: 12837874]

- Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol.* 2007; 27:497–502. [PubMed: 17577648]
- Boztug K, Klein C. Novel genetic etiologies of severe congenital neutropenia. *Curr Opin Immunol.* 2009; 21:472–80. [PubMed: 19782549]
- Boztug K, Klein C. Genetic etiologies of severe congenital neutropenia. *Curr Opin Pediatr.* 2011; 23:21–6. [PubMed: 21206270]
- Boztug K, Schmidt M, Schwarzer A, Banerjee PP, Diez IA, Dewey RA, Bohm M, Nowrouzi A, Ball CR, Glimm H, Naundorf S, Kuhlcke K, Blasczyk R, Kondratenko I, Marodi L, Orange JS, von Kalle C, Klein C. Stem-cell gene therapy for the Wiskott-Aldrich syndrome. *N Engl J Med.* 2010; 363:1918–27. [PubMed: 21067383]
- Brunner C, Muller B, Wirth T. Bruton's Tyrosine Kinase is involved in innate and adaptive immunity. *Histol Histopathol.* 2005; 20:945–55. [PubMed: 15944945]
- Bruton OC. Agammaglobulinemia. *Pediatrics.* 1952; 9:722–8. [PubMed: 14929630]
- Catucci M, Castiello MC, Pala F, Bosticardo M, Villa A. Autoimmunity in wiskott-Aldrich syndrome: an unsolved enigma. *Front Immunol.* 2012; 3:209. [PubMed: 22826711]
- Cengiz MI, Bagci H, Cengiz S, Yigit S, Cengiz K. Periodontal disease in patients with familial Mediterranean fever: from inflammation to amyloidosis. *J Periodontal Res.* 2009; 44:354–61. [PubMed: 18973533]
- Chang CC, Crane M, Zhou J, Mina M, Post JJ, Cameron BA, Lloyd AR, Jaworowski A, French MA, Lewin SR. HIV and co-infections. *Immunol Rev.* 2013; 254:114–42. [PubMed: 23772618]
- Chang MW, Romero R, Scholl PR, Paller AS. Mucocutaneous manifestations of the hyper-IgM immunodeficiency syndrome. *J Am Acad Dermatol.* 1998; 38:191–6. [PubMed: 9486673]
- Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011; 29:4294–301. [PubMed: 21969503]
- Chavez-Garcia AA, Moreno-Alba MA, Elizalde-Monroy M, Segura-Mendez NH, Romero-Flores J, Cambray-Gutierrez JC, Lopez-Perez P, Del Rivero-Hernandez LG. Orofacial clinical manifestations in adult patients with variable common immunodeficiency. *Rev Alerg Mex.* 2015; 62:107–11. [PubMed: 25958373]
- Chen Y, Fang L, Yang X. Cyclic neutropenia presenting as recurrent oral ulcers and periodontitis. *J Clin Pediatr Dent.* 2013; 37:307–8. [PubMed: 23855177]
- Chien HH, Hart TC. Do X-linked diseases affect periodontal health? *Periodontol 2000.* 2013; 61:266–78. [PubMed: 23240954]
- Chinen J, Notarangelo LD, Shearer WT. Advances in basic and clinical immunology in 2012. *J Allergy Clin Immunol.* 2013; 131:675–82. [PubMed: 23374612]
- Chinen J, Shearer WT. 6. Secondary immunodeficiencies, including HIV infection. *J Allergy Clin Immunol.* 2008; 121:S388–92. quiz S417. [PubMed: 18241688]
- Chou JY. The molecular basis of type 1 glycogen storage diseases. *Curr Mol Med.* 2001; 1:25–44. [PubMed: 11899241]
- Chou JY, Sik Jun H, Mansfield BC. The SLC37 family of phosphate-linked sugar phosphate antiporters. *Mol Aspects Med.* 2013; 34:601–11. [PubMed: 23506893]
- Cocco G, Chu DC, Pandolfi S. Colchicine in clinical medicine. A guide for internists. *Eur J Intern Med.* 2010; 21:503–8. [PubMed: 21111934]
- Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cancer WHOIAfRo. Carcinogenicity of human papillomaviruses. *Lancet Oncol.* 2005; 6:204. [PubMed: 15830458]
- Cohen LE, Tanner DJ, Schaefer HG, Levis WR. Common and uncommon cutaneous findings in patients with ataxia-telangiectasia. *J Am Acad Dermatol.* 1984; 10:431–8. [PubMed: 6725655]
- Cohen MS, Leong PA, Simpson DM. Phagocytic cells in periodontal defense. Periodontal status of patients with chronic granulomatous disease of childhood. *J Periodontol.* 1985; 56:611–7. [PubMed: 3863911]

- Cole T, Pearce MS, Cant AJ, Cale CM, Goldblatt D, Gennery AR. Clinical outcome in children with chronic granulomatous disease managed conservatively or with hematopoietic stem cell transplantation. *J Allergy Clin Immunol*. 2013
- Cole TS, Cant AJ. Clinical experience in T cell deficient patients. *Allergy Asthma Clin Immunol*. 2010; 6:9. [PubMed: 20465788]
- Conley, ME., Howard, VC. X-Linked Agammaglobulinemia. In: Pagon, RA, Adam, MP, Bird, TD, Dolan, CR, Fong, CT., Stephens, K., editors. *GeneReviews*. Seattle (WA): 1993.
- Connelly JA, Choi SW, Levine JE. Hematopoietic stem cell transplantation for severe congenital neutropenia. *Curr Opin Hematol*. 2012; 19:44–51. [PubMed: 22080845]
- Cox DP, Weathers DR. Leukocyte adhesion deficiency type I: an important consideration in the clinical differential diagnosis of prepubertal periodontitis. A case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008; 105:86–90. [PubMed: 17618138]
- Cunningham-Rundles C. The many faces of common variable immunodeficiency. *Hematology Am Soc Hematol Educ Program*. 2012; 2012:301–5. [PubMed: 23233596]
- Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999; 92:34–48. [PubMed: 10413651]
- Cutler CW, Jotwani R. Dendritic cells at the oral mucosal interface. *J Dent Res*. 2006; 85:678–89. [PubMed: 16861283]
- Dababneh R, Al-Wahadneh AM, Hamadneh S, Khouri A, Bissada NF. Periodontal manifestation of leukocyte adhesion deficiency type I. *J Periodontol*. 2008; 79:764–8. [PubMed: 18380573]
- Daha MR. Role of complement in innate immunity and infections. *Crit Rev Immunol*. 2010; 30:47–52. [PubMed: 20370619]
- Dahlen G, Bjorkander J, Gahnberg L, Slots J, Hanson LA. Periodontal disease and dental caries in relation to primary IgG subclass and other humoral immunodeficiencies. *J Clin Periodontol*. 1993; 20:7–13. [PubMed: 8421120]
- Dale, DC. ELANE-Related Neutropenia. In: Pagon, RA, Adam, MP, Bird, TD, Dolan, CR, Fong, CT., Stephens, K., editors. *GeneReviews*. Seattle (WA): 1993.
- Dale DC, Cottle TE, Fier CJ, Bolyard AA, Bonilla MA, Boxer LA, Cham B, Freedman MH, Kannourakis G, Kinsey SE, Davis R, Scarlata D, Schwinzer B, Zeidler C, Welte K. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol*. 2003; 72:82–93. [PubMed: 12555210]
- Dale DC, Welte K. Cyclic and chronic neutropenia. *Cancer Treat Res*. 2011; 157:97–108. [PubMed: 21052952]
- Dalgic B, Bukulmez A, Sari S. Eponym: Papillon-Lefevre syndrome. *Eur J Pediatr*. 2011; 170:689–91. [PubMed: 21165749]
- Dalla Torre D, Burtscher D, Jank S, Kloss FR. Necrotizing periodontitis as a possible manifestation of common variable immunodeficiency. *Int J Oral Maxillofac Surg*. 2012; 41:1546–9. [PubMed: 23062717]
- Davoodi P, Hamian M, Nourbaksh R, Ahmadi Motamayel F. Oral Manifestations Related To CD4 Lymphocyte Count in HIV-Positive Patients. *J Dent Res Dent Clin Dent Prospects*. 2010; 4:115–9. [PubMed: 23346337]
- De Cunto C, Britos M, Eymann A, Deltetto N, Liberatore D. Periodic fever: a description of twelve patients with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA). *Arch Argent Pediatr*. 2010; 108:445–8. [PubMed: 21132234]
- de la Morena MT, Nelson RP Jr. Recent Advances in Transplantation for Primary Immune Deficiency Diseases: A Comprehensive Review. *Clin Rev Allergy Immunol*. 2013
- Deas DE, Mackey SA, McDonnell HT. Systemic disease and periodontitis: manifestations of neutrophil dysfunction. *Periodontol*. 2000; 32:82–104. [PubMed: 12756035]
- Deepa D, Kumar KV, Joshi CS, Kumar S, Pandey A. Fungal infection of gingiva in a patient with hyperimmunoglobulin-E (Job's) syndrome. *J Indian Soc Periodontol*. 2012; 16:256–60. [PubMed: 23055595]
- Defraia E, Marinelli A. Oral manifestations of congenital neutropenia or Kostmann syndrome. *J Clin Pediatr Dent*. 2001; 26:99–102. [PubMed: 11688822]

- Delcourt-Debruyne EM, Boutigny HR, Hildebrand HF. Features of severe periodontal disease in a teenager with Chediak-Higashi syndrome. *J Periodontol*. 2000; 71:816–24. [PubMed: 10872965]
- Dincer HE, Dunitz JM. Tracheobronchopathia osteochondroplastica and selective IgA deficiency. *J Bronchology Interv Pulmonol*. 2012; 19:54–6. [PubMed: 23207265]
- Drenth JP, van der Meer JW. Hereditary periodic fever. *N Engl J Med*. 2001; 345:1748–57. [PubMed: 11742050]
- Eapen M, DeLaat CA, Baker KS, Cairo MS, Cowan MJ, Kurtzberg J, Steward CG, Veys PA, Filipovich AH. Hematopoietic cell transplantation for Chediak-Higashi syndrome. *Bone Marrow Transplant*. 2007; 39:411–5. [PubMed: 17293882]
- Engstrom GN, Engstrom PE, Hammarstrom L, Smith CI. Oral conditions in individuals with selective immunoglobulin A deficiency and common variable immunodeficiency. *J Periodontol*. 1992; 63:984–9. [PubMed: 1474470]
- Falcone EL, Holland SM. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. *Curr Opin Infect Dis*. 2012; 25:658–69. [PubMed: 22964947]
- Femiano F, Lanza A, Buonaiuto C, Gombos F, Cirillo N. Oral aphthous-like lesions, PFAPA syndrome: a review. *J Oral Pathol Med*. 2008; 37:319–23. [PubMed: 18221323]
- Fernandes KS, Kokron CM, Barros MT, Kalil J, Gallottini M. Oral manifestations in patients with hypogammaglobulinemia. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012; 114:e19–24.
- Fernandez Lopez MT, Lopez Otero MJ, Alvarez Vazquez P, Arias Delgado J, Varela Correa JJ. Refeeding syndrome. *Farm Hosp*. 2009; 33:183–93. [PubMed: 19712606]
- Fernandez-Banares F, Monzon H, Forne M. A short review of malabsorption and anemia. *World J Gastroenterol*. 2009; 15:4644–52. [PubMed: 19787827]
- Fischer A, Le Deist F, Hacein-Bey-Abina S, Andre-Schmutz I, Basile Gde S, de Villartay JP, Cavazzana-Calvo M. Severe combined immunodeficiency. A model disease for molecular immunology and therapy. *Immunol Rev*. 2005; 203:98–109. [PubMed: 15661024]
- Freeman AF, Domingo DL, Holland SM. Hyper IgE (Job's) syndrome: a primary immune deficiency with oral manifestations. *Oral Dis*. 2009; 15:2–7. [PubMed: 19036057]
- Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. *Clin Microbiol Rev*. 2009; 22:396–414. [PubMed: 19597006]
- Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, Eberschweiler PT, Gajdos V, Labrune P. Glucose-6-phosphatase deficiency. *Orphanet J Rare Dis*. 2011; 6:27. [PubMed: 21599942]
- Fu H, Liu B, Frost JL, Hong S, Jin M, Ostaszewski B, Shankar GM, Costantino IM, Carroll MC, Mayadas TN, Lemere CA. Complement component C3 and complement receptor type 3 contribute to the phagocytosis and clearance of fibrillar A β by microglia. *Glia*. 2012; 60:993–1003. [PubMed: 22438044]
- Fuleihan R, Etzioni A. Primary immunodeficiency diseases: past, present and future. *Curr Opin Allergy Clin Immunol*. 2012; 12:575–6. [PubMed: 23044894]
- Gadola SD, Moins-Teisserenc HT, Trowsdale J, Gross WL, Cerundolo V. TAP deficiency syndrome. *Clin Exp Immunol*. 2000; 121:173–8. [PubMed: 10931128]
- Garcia F, Plana M, Climent N, Leon A, Gatell JM, Gallart T. Dendritic cell based vaccines for HIV infection: The way ahead. *Hum Vaccin Immunother*. 2013; 9
- Gatti R. Ataxia-Telangiectasia. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. *GeneReviews*. Seattle (WA): 1993.
- Gencpinar P, Makay BB, Gattorno M, Caroli F, Unsal E. Mevalonate Kinase Deficiency (Hyper IgD Syndrome with Periodic Fever) - Different Faces with Separate Treatments: Two Cases and Review of the Literature. *Turk J Pediatr*. 2012; 54:641–4. [PubMed: 23692791]
- Gendronneau M, Kerouredan O, Taque S, Sixou JL, Bonnaure-Mallet M. Dental abnormalities and preventive oral care in Schimke immuno-osseous dysplasia. *Eur Arch Paediatr Dent*. 2014; 15:217–21. [PubMed: 24327104]
- Gennery AR. Immunological aspects of 22q11.2 deletion syndrome. *Cell Mol Life Sci*. 2012; 69:17–27. [PubMed: 21984609]

- Goultschin J, Attal U, Goldstein M, Boyan BD, Schwartz Z. The relationship between peripheral levels of leukocytes and neutrophils and periodontal disease status in a patient with congenital neutropenia. *J Periodontol*. 2000; 71:1499–505. [PubMed: 11022781]
- Grattagliano I, Bonfrate L, Ruggiero V, Scaccianoce G, Palasciano G, Portincasa P. Novel Therapeutics for the Treatment of Familial Mediterranean Fever: From Colchicine to Biologics. *Clin Pharmacol Ther*. 2013
- Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, Miller JA, O'Connell AC, Puck JM. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med*. 1999; 340:692–702. [PubMed: 10053178]
- Grumach AS, Duarte AJ, Bellinati-Pires R, Pastorino AC, Jacob CM, Diogo CL, Condino-Neto A, Kirschfink M, Carneiro-Sampaio MM. Brazilian report on primary immunodeficiencies in children: 166 cases studied over a follow-up time of 15 years. *J Clin Immunol*. 1997; 17:340–5. [PubMed: 9258773]
- Grunebaum E, Mazzolari E, Porta F, Dallera D, Atkinson A, Reid B, Notarangelo LD, Roifman CM. Bone marrow transplantation for severe combined immune deficiency. *JAMA*. 2006; 295:508–18. [PubMed: 16449616]
- Guirrat-Dhouib N, Baccar Y, Mustapha IB, Ouederni M, Chouaibi S, El Fekih N, Barbouche MR, Fezaa B, Kouki R, Hmida S, Mellouli F, Bejaoui M. Oral HPV infection and MHC class II deficiency (A study of two cases with atypical outcome). *Clin Mol Allergy*. 2012; 10:6. [PubMed: 22524894]
- Gunhan O, Celasun B, Perrini F, Covani U, Perrini N, Ozdemir A, Bostanci H, Finci R. Generalized gingival enlargement due to accumulation of amyloid-like material. *J Oral Pathol Med*. 1994; 23:423–8. [PubMed: 7823304]
- Gunhan O, Gunhan M, Berker E, Gurgan CA, Yildirim H. Destructive membranous periodontal disease (Ligneous periodontitis). *J Periodontol*. 1999; 70:919–25. [PubMed: 10476902]
- Gupta KB, Gupta R, Atreja A, Verma M, Vishvkarma S. Tuberculosis and nutrition. *Lung India*. 2009; 26:9–16. [PubMed: 20165588]
- Hagensee ME, Cameron JE, Leigh JE, Clark RA. Human papillomavirus infection and disease in HIV-infected individuals. *Am J Med Sci*. 2004; 328:57–63. [PubMed: 15254442]
- Hajishengallis G. Complement and periodontitis. *Biochem Pharmacol*. 2010; 80:1992–2001. [PubMed: 20599785]
- Hakki SS, Aprikyan AA, Yildirim S, Aydinbelge M, Gokalp A, Ucar C, Guran S, Koseoglu V, Ataoglu T, Somerman MJ. Periodontal status in two siblings with severe congenital neutropenia: diagnosis and mutational analysis of the cases. *J Periodontol*. 2005; 76:837–44. [PubMed: 15898946]
- Hamilton RE Jr, Giansanti JS. The Chediak-Higashi syndrome. Report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol*. 1974; 37:754–61. [PubMed: 4524383]
- Hanna S, Etzioni A. Leukocyte adhesion deficiencies. *Ann N Y Acad Sci*. 2012; 1250:50–5. [PubMed: 22276660]
- Hart TC, Shapira L, Van Dyke TE. Neutrophil defects as risk factors for periodontal diseases. *J Periodontol*. 1994; 65:521–9. [PubMed: 8046568]
- Hart TC, Stabholz A, Meyle J, Shapira L, Van Dyke TE, Cutler CW, Soskolne WA. Genetic studies of syndromes with severe periodontitis and palmoplantar hyperkeratosis. *J Periodontol Res*. 1997; 32:81–9. [PubMed: 9085215]
- Hassan A, Booth C, Brightwell A, Allwood Z, Veys P, Rao K, Honig M, Friedrich W, Gennery A, Slatter M, Bredius R, Finocchi A, Cancrini C, Aiuti A, Porta F, Lanfranchi A, Ridella M, Steward C, Filipovich A, Marsh R, Bordon V, Al-Muhsen S, Al-Mousa H, Alsum Z, Al-Dhekri H, Al Ghonaum A, Speckmann C, Fischer A, Mahlaoui N, Nichols KE, Grunebaum E, Al Zaharani D, Roifman CM, Boelens J, Davies EG, Cavazzana-Calvo M, Notarangelo L, Gaspar HB, Inborn Errors Working Party of the European Group for B, Marrow T and European Society for I. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. *Blood*. 2012; 120:3615–24. quiz 3626. [PubMed: 22791287]

- Hasturk H, Tezcan I, Yel L, Ersoy F, Sanal O, Yamalik N, Berker E. A case of chronic severe neutropenia: oral findings and consequences of short-term granulocyte colony-stimulating factor treatment. *Aust Dent J*. 1998; 43:9–13. [PubMed: 9583218]
- Hatori M, Yoshiya M, Kurachi Y, Nagumo M. Prolonged infection of the floor of the mouth in hyperimmunoglobulinemia E (Buckley's syndrome). Report of a case. *Oral Surg Oral Med Oral Pathol*. 1993; 76:289–93. [PubMed: 8378042]
- Heimall J, Freeman A, Holland SM. Pathogenesis of hyper IgE syndrome. *Clin Rev Allergy Immunol*. 2010; 38:32–8. [PubMed: 19452285]
- Henriet S, Verweij PE, Holland SM, Warris A. Invasive fungal infections in patients with chronic granulomatous disease. *Adv Exp Med Biol*. 2013; 764:27–55. [PubMed: 23654055]
- Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, Porras C, Schiffman M, Rodriguez AC, Solomon D, Jimenez S, Schiller JT, Lowy DR, van Doorn LJ, Wacholder S, Kreimer AR, Group CVTV. Reduced Prevalence of Oral Human Papillomavirus (HPV) 4 Years after Bivalent HPV Vaccination in a Randomized Clinical Trial in Costa Rica. *PLoS One*. 2013; 8:e68329. [PubMed: 23873171]
- Hofmann SR, Roesen-Wolff A, Hahn G, Hedrich CM. Update: Cytokine Dysregulation in Chronic Nonbacterial Osteomyelitis (CNO). *Int J Rheumatol*. 2012; 2012:310206. [PubMed: 22685464]
- Horwitz MS, Corey SJ, Grimes HL, Tidwell T. ELANE mutations in cyclic and severe congenital neutropenia: genetics and pathophysiology. *Hematol Oncol Clin North Am*. 2013; 27:19–41, vii. [PubMed: 23351986]
- Horwitz MS, Duan Z, Korkmaz B, Lee HH, Mealiffe ME, Salipante SJ. Neutrophil elastase in cyclic and severe congenital neutropenia. *Blood*. 2007; 109:1817–24. [PubMed: 17053055]
- Huppler AR, Bishu S, Gaffen SL. Mucocutaneous candidiasis: the IL-17 pathway and implications for targeted immunotherapy. *Arthritis Res Ther*. 2012; 14:217. [PubMed: 22838497]
- Introne W, Boissy RE, Gahl WA. Clinical, molecular, and cell biological aspects of Chediak-Higashi syndrome. *Mol Genet Metab*. 1999; 68:283–303. [PubMed: 10527680]
- Jain A, Kovacs JA, Nelson DL, Migueles SA, Pittaluga S, Fanslow W, Fan X, Wong DW, Massey J, Hornung R, Brown MR, Spinner JJ, Liu S, Davey V, Hill HA, Ochs H, Fleisher TA. Partial immune reconstitution of X-linked hyper IgM syndrome with recombinant CD40 ligand. *Blood*. 2011; 118:3811–7. [PubMed: 21841160]
- Java A, Atkinson J, Salmon J. Defective complement inhibitory function predisposes to renal disease. *Annu Rev Med*. 2013; 64:307–24. [PubMed: 23121180]
- Jayasinghe M, Schmidt S, Walker B, Rocken M, Schaller M. Successful treatment of azole-resistant chronic mucocutaneous candidosis with caspofungin. *Acta Derm Venereol*. 2006; 86:563–4. [PubMed: 17106615]
- Johnson NW. The mouth in HIV/AIDS: markers of disease status and management challenges for the dental profession. *Aust Dent J*. 2010; 55(Suppl 1):85–102. [PubMed: 20553249]
- Jorgensen GH, Arnlaugsson S, Theodors A, Ludviksson BR. Immunoglobulin A deficiency and oral health status: a case-control study. *J Clin Periodontol*. 2010; 37:1–8. [PubMed: 19968742]
- Jorgensen GH, Gardulf A, Sigurdsson MI, Sigurdardottir ST, Thorsteinsdottir I, Gudmundsson S, Hammarstrom L, Ludviksson BR. Clinical symptoms in adults with selective IgA deficiency: a case-control study. *J Clin Immunol*. 2013; 33:742–7. [PubMed: 23389234]
- Jotwani R, Cutler CW. Multiple dendritic cell (DC) subpopulations in human gingiva and association of mature DCs with CD4+ T-cells in situ. *J Dent Res*. 2003; 82:736–41. [PubMed: 12939360]
- Jotwani R, Muthukuru M, Cutler CW. Increase in HIV receptors/co-receptors/alpha-defensins in inflamed human gingiva. *J Dent Res*. 2004; 83:371–7. [PubMed: 15111627]
- Jotwani R, Palucka AK, Al-Quotub M, Nouri-Shirazi M, Kim J, Bell D, Banchereau J, Cutler CW. Mature dendritic cells infiltrate the T cell-rich region of oral mucosa in chronic periodontitis: in situ, in vivo, and in vitro studies. *J Immunol*. 2001; 167:4693–700. [PubMed: 11591800]
- Kadlub N, Vazquez MP, Galmiche L, L'Hermine AC, Dainese L, Ulinski T, Fauroux B, Pavlov I, Badoual C, Marlin S, Deckert M, Leboulanger N, Berdal A, Descroix V, Picard A, Coudert AE. The calcineurin inhibitor tacrolimus as a new therapy in severe cherubism. *J Bone Miner Res*. 2015; 30:878–85. [PubMed: 25491283]
- Kannourakis G. Glycogen storage disease. *Semin Hematol*. 2002; 39:103–6. [PubMed: 11957192]

- Kanthimathinathan HK, Browne F, Ramirez R, McKaig S, Debelle G, Martin J, Chapple IL, Kay A, Moss C. Multiple cerebral abscesses in Papillon-Lefevre syndrome. *Childs Nerv Syst.* 2013; 29:1227–9. [PubMed: 23686359]
- Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. *Curr Opin Hematol.* 2008; 15:22–9. [PubMed: 18043242]
- Karaca NE, Aksu G, Gulez N, Yildiz B, Azarsiz E, Kutukculer N. New laboratory findings in Turkish patients with transient hypogammaglobulinemia of infancy. *Iran J Allergy Asthma Immunol.* 2010; 9:237–43. [PubMed: 21131704]
- Keles S, Artac H, Kara R, Gokturk B, Ozen A, Reisli I. Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: 'similarities and differences'. *Pediatr Allergy Immunol.* 2010; 21:843–51. [PubMed: 20609138]
- Keskin-Yildirim Z, Simsek-Derelioglu S, Kantarci M, Yilmaz Y, Buyukavci M. Papillon-Lefevre syndrome: report of three cases in the same family. *Turk J Pediatr.* 2012; 54:171–6. [PubMed: 22734305]
- Khoht A, Viera-Negron YE, Ameri A, Abdelsayed R. Periodontitis associated with Chediak-Higashi syndrome in a young African American male. *J Int Acad Periodontol.* 2010; 12:49–55. [PubMed: 20465032]
- Kilic SS, Tezcan I, Sanal O, Metin A, Ersoy F. Transient hypogammaglobulinemia of infancy: clinical and immunologic features of 40 new cases. *Pediatr Int.* 2000; 42:647–50. [PubMed: 11192522]
- Klingberg G, Oskarsdottir S, Johannesson EL, Noren JG. Oral manifestations in 22q11 deletion syndrome. *Int J Paediatr Dent.* 2002; 12:14–23. [PubMed: 11853243]
- Kluger N, Jokinen M, Krohn K, Ranki A. Gastrointestinal manifestations in APECED syndrome. *J Clin Gastroenterol.* 2013; 47:112–20. [PubMed: 23314667]
- Kolly L, Busso N, von Scheven-Gete A, Bagnoud N, Moix I, Holzinger D, Simon G, Ives A, Guarda G, So A, Morris MA, Hofer M. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome is linked to dysregulated monocyte IL-1 β production. *J Allergy Clin Immunol.* 2013; 131:1635–43. [PubMed: 23006543]
- Korkmaz C. Therapeutic approach to patients with familial Mediterranean fever-related amyloidosis resistant to colchicine. *Clin Exp Rheumatol.* 2012; 30:S104–7.
- Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol.* 2009; 27:485–517. [PubMed: 19132915]
- Korppi M, Van Gijn ME, Antila K. Hyperimmunoglobulinemia D and periodic fever syndrome in children. Review on therapy with biological drugs and case report. *Acta Paediatr.* 2011; 100:21–5. [PubMed: 20712835]
- Krentz HB, Kliwer G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Med.* 2005; 6:99–106. [PubMed: 15807715]
- Kretschmer S, Wolf C, Konig N, Staroske W, Guck J, Hausler M, Luksch H, Nguyen LA, Kim B, Alexopoulou D, Dahl A, Rapp A, Cardoso MC, Shevchenko A, Lee-Kirsch MA. SAMHD1 prevents autoimmunity by maintaining genome stability. *Ann Rheum Dis.* 2015; 74:e17. [PubMed: 24445253]
- Laguette N, Sobhian B, Casartelli N, Ringiard M, Chable-Bessia C, Segéral E, Yatim A, Emiliani S, Schwartz O, Benkirane M. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. *Nature.* 2011; 474:654–7. [PubMed: 21613998]
- Lane T, Loeffler JM, Rowczenio DM, Gilbertson JA, Bybee A, Russell TL, Gillmore JD, Wechalekar AD, Hawkins PN, Lachmann HJ. AA amyloidosis complicating the hereditary periodic fever syndromes. *Arthritis Rheum.* 2013; 65:1116–21. [PubMed: 23280696]
- Lee YM, Jun HS, Pan CJ, Lin SR, Wilson LH, Mansfield BC, Chou JY. Prevention of hepatocellular adenoma and correction of metabolic abnormalities in murine glycogen storage disease type Ia by gene therapy. *Hepatology.* 2012; 56:1719–29. [PubMed: 22422504]
- Lehman JS, Bruce AJ, Rogers RS. Atrophic glossitis from vitamin B12 deficiency: a case misdiagnosed as burning mouth disorder. *J Periodontol.* 2006; 77:2090–2. [PubMed: 17209796]
- Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, Sanders EA, Tabone MD, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom

- L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD. Clinical spectrum of X-linked hyper-IgM syndrome. *J Pediatr*. 1997; 131:47–54. [PubMed: 9255191]
- Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol*. 2007; 7:678–89. [PubMed: 17717539]
- Licameli G, Lawton M, Kenna M, Dedeoglu F. Long-term surgical outcomes of adenotonsillectomy for PFAPA syndrome. *Arch Otolaryngol Head Neck Surg*. 2012; 138:902–6. [PubMed: 23069819]
- Lin CM, Wang CC, Lai CC, Fan HC, Huang WH, Cheng SN. Genital ulcers as an unusual sign of periodic fever, aphthous stomatitis, pharyngotonsillitis, cervical adenopathy syndrome: a novel symptom? *Pediatr Dermatol*. 2011; 28:290–4. [PubMed: 21133994]
- Liu X, Hua H. Oral manifestation of chronic mucocutaneous candidiasis: seven case reports. *J Oral Pathol Med*. 2007; 36:528–32. [PubMed: 17850435]
- Lopez-Jornet P, Garcia-Ballesta C, Perez-Lajarin L. Mucocutaneous candidiasis as first manifestation of autoimmune polyglandular syndrome type I. *J Dent Child (Chic)*. 2005; 72:21–4. [PubMed: 16119071]
- Lu RF, Meng HX. Severe periodontitis in a patient with cyclic neutropenia: a case report of long-term follow-up. *Chin J Dent Res*. 2012; 15:159–63. [PubMed: 23509838]
- Lu SY, Wu HC. Initial diagnosis of anemia from sore mouth and improved classification of anemias by MCV and RDW in 30 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004; 98:679–85. [PubMed: 15583540]
- Lutskiy MI, Sasahara Y, Kenney DM, Rosen FS, Remold-O'Donnell E. Wiskott-Aldrich syndrome in a female. *Blood*. 2002; 100:2763–8. [PubMed: 12351383]
- Maehara T, Moriyama M, Kawano S, Hayashida JN, Furukawa S, Ohta M, Tanaka A, Yamauchi M, Ohyama Y, Kiyoshima T, Nakamura S. Cytokine profiles contribute to understanding the pathogenic difference between Good syndrome and oral lichen planus: two case reports and literature review. *Medicine (Baltimore)*. 2015; 94:e704. [PubMed: 25860215]
- Mahlaoui N, Pellier I, Mignot C, Jais JP, Bilhou-Nabera C, Moshous D, Neven B, Picard C, de Saint-Basile G, Cavazzana-Calvo M, Blanche S, Fischer A. Characteristics and outcome of early-onset, severe forms of Wiskott-Aldrich syndrome. *Blood*. 2013; 121:1510–6. [PubMed: 23264593]
- Majorana A, Notarangelo LD, Savoldi E, Gastaldi G, Lozada-Nur F. Leukocyte adhesion deficiency in a child with severe oral involvement. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 87:691–4. [PubMed: 10397659]
- Malech HL, Ochs HD. An emerging era of clinical benefit from gene therapy. *JAMA*. 2015; 313:1522–3. [PubMed: 25898049]
- Marom T, Roth Y, Goldfarb A, Cinamon U. Head and neck manifestations of 22q11.2 deletion syndromes. *Eur Arch Otorhinolaryngol*. 2012; 269:381–7. [PubMed: 21861138]
- Marron TU, Martinez-Gallo M, Yu JE, Cunningham-Rundles C. Toll-like receptor 4-, 7-, and 8-activated myeloid cells from patients with X-linked agammaglobulinemia produce enhanced inflammatory cytokines. *J Allergy Clin Immunol*. 2012; 129:184–90. e1–4. [PubMed: 22088613]
- Marsman WA, Sukhai RN. Recurrent parotitis and isolated IgG3 subclass deficiency. *Eur J Pediatr*. 1999; 158:684. [PubMed: 10445352]
- Massaad MJ, Ramesh N, Geha RS. Wiskott-Aldrich syndrome: a comprehensive review. *Ann N Y Acad Sci*. 2013; 1285:26–43. [PubMed: 23527602]
- Mataftsi M, Skoura L, Sakellari D. HIV infection and periodontal diseases: an overview of the post-HAART era. *Oral Dis*. 2011; 17:13–25. [PubMed: 21029260]
- Mavroudi I, Papadaki HA. The role of CD40/CD40 ligand interactions in bone marrow granulopoiesis. *ScientificWorldJournal*. 2011; 11:2011–9. [PubMed: 22125452]
- McCusker C, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol*. 2011; 7(Suppl 1):S11. [PubMed: 22165913]
- McDonald DR. TH17 deficiency in human disease. *J Allergy Clin Immunol*. 2012; 129:1429–35. quiz 1436–7. [PubMed: 22554706]

- McKenna G, Ziada H, Allen PF. Prosthodontic rehabilitation of a patient using a swing-lock lower denture after segmental mandibulectomy. *Eur J Prosthodont Restor Dent*. 2013; 21:141–4. [PubMed: 24261107]
- McLaren DS. Vitamin A deficiency disorders. *J Indian Med Assoc*. 1999; 97:320–3. [PubMed: 10643184]
- Meighani G, Aghamohammadi A, Javanbakht H, Abolhassani H, Nikayin S, Jafari SM, Ghandehari Motlagh M, Shamshiri AR, Rezaei N. Oral and dental health status in patients with primary antibody deficiencies. *Iran J Allergy Asthma Immunol*. 2011; 10:289–93. [PubMed: 22184272]
- Menasche G, Feldmann J, Fischer A, de Saint Basile G. Primary hemophagocytic syndromes point to a direct link between lymphocyte cytotoxicity and homeostasis. *Immunol Rev*. 2005; 203:165–79. [PubMed: 15661029]
- Meyle J. Leukocyte adhesion deficiency and prepubertal periodontitis. *Periodontol* 2000. 1994; 6:26–36. [PubMed: 9673168]
- Mialou V, Leblanc T, Peffault de Latour R, Dalle JH, Socie G. Dyskeratosis congenita: an update. *Arch Pediatr*. 2013; 20:299–306. [PubMed: 23352883]
- Micol R, Ben Slama L, Suarez F, Le Mignot L, Beaute J, Mahlaoui N, Dubois d'Enghien C, Lauge A, Hall J, Couturier J, Vallee L, Delobel B, Rivier F, Nguyen K, Billette de Villemeur T, Stephan JL, Bordigoni P, Bertrand Y, Aladjidi N, Pedespan JM, Thomas C, Pellier I, Koenig M, Hermine O, Picard C, Moshous D, Neven B, Lanternier F, Blanche S, Tardieu M, Debre M, Fischer A, Stoppa-Lyonnet D, Investigators CN. Morbidity and mortality from ataxia-telangiectasia are associated with ATM genotype. *J Allergy Clin Immunol*. 2011; 128:382–9 e1. [PubMed: 21665257]
- Millar S, Carson D. Clinical phenotypes of autoimmune polyendocrinopathycandidiasis-ectodermal dystrophy seen in the Northern Ireland paediatric population over the last 30 years. *Ulster Med J*. 2012; 81:118–22. [PubMed: 23620608]
- Mitsui H, Komine M, Shirai A, Kanda N, Asahina A, Okochi H, Hitomi S, Kimura S, Tamaki K. Chronic active EB virus infection complicated with IgG3 subclass deficiency: an adult case treated with intravenous immunoglobulin and IFN-alpha. *Acta Derm Venereol*. 2003; 83:31–5. [PubMed: 12636019]
- Morgan RD, Hannon E, Lakhoo K. Renal abscess in Papillion-Lefevre syndrome. *Pediatr Surg Int*. 2011; 27:1381–3. [PubMed: 21594717]
- Morimoto, M., Baradaran-Heravi, A., Lucke, T., Boerkoel, CF. *Schimke Immunoosseous Dysplasia*. In: Pagon, RA, Adam, MP, Ardinger, HH, Wallace, SE, Amemiya, A, Bean, LJH, Bird, TD, Dolan, CR, Fong, CT, Smith, RJH., Stephens, K., editors. *GeneReviews(R)*. Seattle (WA): 1993.
- Morimoto M, Kerouredan O, Gendronneau M, Shuen C, Baradaran-Heravi A, Asakura Y, Basiratnia M, Bogdanovic R, Bonneau D, Buck A, Charrow J, Cochat P, Dehaai KA, Fenkci MS, Frange P, Frund S, Fryssira H, Keller K, Kirmani S, Kobelka C, Kohler K, Lewis DB, Massella L, McLeod DR, Milford DV, Nobili F, Olney AH, Semerci CN, Stajic N, Stein A, Taque S, Zonana J, Lucke T, Henderson G, Bonnaure-Mallet M, Boerkoel CF. Dental abnormalities in Schimke immunoosseous dysplasia. *J Dent Res*. 2012; 91:29S–37S. [PubMed: 22699664]
- Morio T. Common variable immunodeficiency. *Nihon Rinsho*. 2012; 70:2011–21. [PubMed: 23214077]
- Mortellaro C, Garagiola U, Carbone V, Cerutti F, Marci V, Bonda PL. Unusual oral manifestations and evolution in glycogen storage disease type Ib. *J Craniofac Surg*. 2005; 16:45–52. [PubMed: 15699644]
- Moschese V, Graziani S, Avanzini MA, Carsetti R, Marconi M, La Rocca M, Chini L, Pignata C, Soresina AR, Consolini R, Bossi G, Trizzino A, Martino S, Cardinale F, Bertolini P, Marseglia GL, Zecca M, Di Cesare S, Quinti I, Rondelli R, Pietrogrande MC, Rossi P, Plebani A. A prospective study on children with initial diagnosis of transient hypogammaglobulinemia of infancy: results from the Italian Primary Immunodeficiency Network. *Int J Immunopathol Pharmacol*. 2008; 21:343–52. [PubMed: 18547478]
- Murata T, Okamoto N, Shimizu T, Tamai H. Diagnosis and management of periodic fever with aphthous pharyngitis and adenitis (PFAPA). *Nihon Rinsho Meneki Gakkai Kaishi*. 2007; 30:101–7. [PubMed: 17473512]

- Muscari I, Iacoponi F, Cantarini L, Lucherini OM, Simonini G, Brizi MG, Vitale A, Frediani B, Cimaz R, Galeazzi M. The diagnostic evaluation of patients with potential adult-onset autoinflammatory disorders: our experience and review of the literature. *Autoimmun Rev*. 2012; 12:10–3. [PubMed: 22878268]
- Myhre AG, Stray-Pedersen A, Spangen S, Eide E, Veimo D, Knappskog PM, Abrahamsen TG, Husebye ES. Chronic mucocutaneous candidiasis and primary hypothyroidism in two families. *Eur J Pediatr*. 2004; 163:604–11. [PubMed: 15290270]
- Myllarniemi S, Perheentupa J. Oral findings in the autoimmune polyendocrinopathy-candidosis syndrome (APECs) and other forms of hypoparathyroidism. *Oral Surg Oral Med Oral Pathol*. 1978; 45:721–9. [PubMed: 276791]
- Nagendran J, Prakash C, Anandakrishna L, Gaviappa D, Ganesh D. Leukocyte adhesion deficiency: a case report and review. *J Dent Child (Chic)*. 2012; 79:105–10. [PubMed: 22828768]
- Nakajima K, Nakano H, Takiyoshi N, Rokunohe A, Ikenaga S, Aizu T, Kaneko T, Mitsushashi Y, Sawamura D. Papillon-Lefevre syndrome and malignant melanoma. A high incidence of melanoma development in Japanese palmoplantar keratoderma patients. *Dermatology*. 2008; 217:58–62. [PubMed: 18401176]
- Nickles K, Schacher B, Ratka-Kruger P, Krebs M, Eickholz P. Long-term results after treatment of periodontitis in patients with Papillon-Lefevre syndrome: success and failure. *J Clin Periodontol*. 2013; 40:789–98. [PubMed: 23829197]
- Nikfarjam J, Pourpak Z, Shahrabi M, Nikfarjam L, Kouhkan A, Moazeni M, Aghamohammadi A. Oral manifestations in selective IgA deficiency. *Int J Dent Hyg*. 2004; 2:19–25. [PubMed: 16451448]
- Nordgarden H, Lima K, Skogedal N, Folling I, Storhaug K, Abrahamsen TG. Dental developmental disturbances in 50 individuals with the 22q11.2 deletion syndrome; relation to medical conditions? *Acta Odontol Scand*. 2012; 70:194–201. [PubMed: 22070626]
- Notarangelo LD. Functional T cell immunodeficiencies (with T cells present). *Annu Rev Immunol*. 2013; 31:195–225. [PubMed: 23298211]
- Notarangelo LD, Badolato R. Leukocyte trafficking in primary immunodeficiencies. *J Leukoc Biol*. 2009; 85:335–43. [PubMed: 19088178]
- Notarangelo LD, Duse M, Ugazio AG. Immunodeficiency with hyper-IgM (HIM). *Immunodef Rev*. 1992; 3:101–21. [PubMed: 1554497]
- Notarangelo LD, Miao CH, Ochs HD. Wiskott-Aldrich syndrome. *Curr Opin Hematol*. 2008; 15:30–6. [PubMed: 18043243]
- Ocampo CJ, Peters AT. Antibody deficiency in chronic rhinosinusitis: epidemiology and burden of illness. *Am J Rhinol Allergy*. 2013; 27:34–8. [PubMed: 23406598]
- Olinder-Nielsen AM, Granert C, Forsberg P, Friman V, Vietorisz A, Bjorkander J. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. *Scand J Infect Dis*. 2007; 39:44–50. [PubMed: 17366012]
- Olmedo JM, Yiannias JA, Windgassen EB, Gornet MK. Scurvy: a disease almost forgotten. *Int J Dermatol*. 2006; 45:909–13. [PubMed: 16911372]
- Oxelius VA, Hanson LA, Bjorkander J, Hammarstrom L, Sjöholm A. IgG3 deficiency: common in obstructive lung disease. Hereditary in families with immunodeficiency and autoimmune disease. *Monogr Allergy*. 1986; 20:106–15. [PubMed: 3773900]
- Padeh S, Stoffman N, Berkun Y. Periodic fever accompanied by aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome) in adults. *Isr Med Assoc J*. 2008; 10:358–60. [PubMed: 18605359]
- Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD, Investigators HIVOS. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006; 43:27–34. [PubMed: 16878047]
- Panayiotopoulos A, Bhat N, Bhangoo A. Bone and vitamin D metabolism in HIV. *Rev Endocr Metab Disord*. 2013; 14:119–25. [PubMed: 23657562]
- Patton L, Ramirez-Amador V, Anaya-Saavedra G, Nittayananta W, Carrozzo M, Ranganathan K. Urban legends series: oral manifestations of HIV infection. *Oral Dis*. 2013; 19:533–50. [PubMed: 23517181]

- Perez-Aguilar MC, Goncalves L, Bonfante-Cabarcas R. Adenosine deaminase in severe combined immunodeficiency syndrome. *Invest Clin*. 2012; 53:315–24. [PubMed: 23248974]
- Pernu HE, Pajari UH, Lanning M. The importance of regular dental treatment in patients with cyclic neutropenia. Follow-up of 2 cases. *J Periodontol*. 1996; 67:454–9. [PubMed: 8708974]
- Phiri R, Feller L, Blignaut E. The severity, extent and recurrence of necrotizing periodontal disease in relation to HIV status and CD4+ T cell count. *J Int Acad Periodontol*. 2010; 12:98–103. [PubMed: 21128527]
- Pinto A, Lindemeyer RG, Sollecito TP. The PFAPA syndrome in oral medicine: differential diagnosis and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006; 102:35–9. [PubMed: 16831670]
- Porter SR, Eveson JW, Scully C. Enamel hypoplasia secondary to candidiasis endocrinopathy syndrome: case report. *Pediatr Dent*. 1995; 17:216–9. [PubMed: 7617499]
- Porter SR, Scully C. Orofacial manifestations in primary immunodeficiencies involving IgA deficiency. *J Oral Pathol Med*. 1993a; 22:117–9. [PubMed: 8487217]
- Porter SR, Scully C. Orofacial manifestations in primary immunodeficiencies: common variable immunodeficiencies. *J Oral Pathol Med*. 1993b; 22:157–8. [PubMed: 8315594]
- Porter SR, Scully C. Orofacial manifestations in the primary immunodeficiency disorders. *Oral Surg Oral Med Oral Pathol*. 1994; 78:4–13. [PubMed: 8078661]
- Porter SR, Sugerman PB, Scully C, Luker J, Oakhill A. Orofacial manifestations in the Wiskott-Aldrich syndrome. *ASDC J Dent Child*. 1994; 61:404–7. [PubMed: 7897015]
- Proust-Lemoine E, Saugier-Verber P, Wemeau JL. Polyglandular autoimmune syndrome type I. *Presse Med*. 2012; 41:e651–62. [PubMed: 23182677]
- Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol*. 2012; 12:616–22. [PubMed: 23026768]
- Qamar N, Fuleihan RL. The Hyper IgM Syndromes. *Clin Rev Allergy Immunol*. 2013
- Qian JH, Zhu JX, Zhu XD, Chen TX. Clinical features and follow-up of Chinese patients with symptomatic hypogammaglobulinemia in infancy. *Chin Med J (Engl)*. 2009; 122:1877–83. [PubMed: 19781364]
- Quinti I, Agostini C, Tabolli S, Brunetti G, Cinetto F, Pecoraro A, Spadaro G. Malignancies are the major cause of death in patients with adult onset common variable immunodeficiency. *Blood*. 2012; 120:1953–4. [PubMed: 22936739]
- Rajas F, Labrune P, Mithieux G. Glycogen storage disease type 1 and diabetes: Learning by comparing and contrasting the two disorders. *Diabetes Metab*. 2013
- Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. *Clin Microbiol Rev*. 2010; 23:740–80. [PubMed: 20930072]
- Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood*. 2012; 119:1650–7. [PubMed: 22180439]
- Rezaei N, Farhoudi A, Ramyar A, Pourpak Z, Aghamohammadi A, Mohammadpour B, Moin M, Gharagozlou M, Movahedi M, Ghazi BM, Izadyar M, Mahmoudi M. Congenital neutropenia and primary immunodeficiency disorders: a survey of 26 Iranian patients. *J Pediatr Hematol Oncol*. 2005; 27:351–6. [PubMed: 16012323]
- Rezaei N, Moazzami K, Aghamohammadi A, Klein C. Neutropenia and primary immunodeficiency diseases. *Int Rev Immunol*. 2009; 28:335–66. [PubMed: 19811314]
- Rezaei N, Moin M, Pourpak Z, Ramyar A, Izadyar M, Chavoshzadeh Z, Sherkat R, Aghamohammadi A, Yeganeh M, Mahmoudi M, Mahjoub F, Germeshausen M, Grudzien M, Horwitz MS, Klein C, Farhoudi A. The clinical, immunohematological, and molecular study of Iranian patients with severe congenital neutropenia. *J Clin Immunol*. 2007; 27:525–33. [PubMed: 17587155]
- Robertson PB, Mackler BF, Wright TE, Levy BM. Periodontal status of patients with abnormalities of the immune system. II. Observations over a 2-year period. *J Periodontol*. 1980; 51:70–3. [PubMed: 6928473]
- Roifman CM, Somech R, Kavadas F, Pires L, Nahum A, Dalal I, Grunebaum E. Defining combined immunodeficiency. *J Allergy Clin Immunol*. 2012; 130:177–83. [PubMed: 22664165]

- Roos D, de Boer M, Kuribayashi F, Meischl C, Weening RS, Segal AW, Ahlin A, Nemet K, Hossle JP, Bernatowska-Matuszkiewicz E, Middleton-Price H. Mutations in the X-linked and autosomal recessive forms of chronic granulomatous disease. *Blood*. 1996; 87:1663–81. [PubMed: 8634410]
- Sakai H, Heike T. Hyperimmunoglobulinemia D and periodic fever syndrome. *Nihon Rinsho Meneki Gakkai Kaishi*. 2011; 34:382–7. [PubMed: 22041426]
- Salapata Y, Laskaris G, Drogari E, Harokopos E, Messaritakis J. Oral manifestations in glycogen storage disease type 1b. *J Oral Pathol Med*. 1995; 24:136–9. [PubMed: 7776266]
- Saleem MA, Arkwright PD, Davies EG, Cant AJ, Veys PA. Clinical course of patients with major histocompatibility complex class II deficiency. *Arch Dis Child*. 2000; 83:356–9. [PubMed: 10999878]
- Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency - an update. *Arthritis Res Ther*. 2012; 14:223. [PubMed: 23043756]
- Sampaio EP, Bax HI, Hsu AP, Kristosturyan E, Pechacek J, Chandrasekaran P, Paulson ML, Dias DL, Spalding C, Uzel G, Ding L, McFarland E, Holland SM. A novel STAT1 mutation associated with disseminated mycobacterial disease. *J Clin Immunol*. 2012; 32:681–9. [PubMed: 22437822]
- Sampaio EP, Hsu AP, Pechacek J, Bax HI, Dias DL, Paulson ML, Chandrasekaran P, Rosen LB, Carvalho DS, Ding L, Vinh DC, Browne SK, Datta S, Milner JD, Kuhns DB, Long Priel DA, Sadat MA, Shiloh M, De Marco B, Alvares M, Gillman JW, Ramarathnam V, de la Morena M, Bezrodnik L, Moreira I, Uzel G, Johnson D, Spalding C, Zerbe CS, Wiley H, Greenberg DE, Hoover SE, Rosenzweig SD, Galgiani JN, Holland SM. Signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations and disseminated coccidioidomycosis and histoplasmosis. *J Allergy Clin Immunol*. 2013; 131:1624–34. [PubMed: 23541320]
- Saunders J, Smith T. Malnutrition: causes and consequences. *Clin Med*. 2010; 10:624–7.
- Savage SA, Bertuch AA. The genetics and clinical manifestations of telomere biology disorders. *Genet Med*. 2010; 12:753–64. [PubMed: 21189492]
- Savic S, Dickie LJ, Battellino M, McDermott MF. Familial Mediterranean fever and related periodic fever syndromes/autoinflammatory diseases. *Curr Opin Rheumatol*. 2012; 24:103–12. [PubMed: 22089100]
- Schmidt S, Moser M, Sperandio M. The molecular basis of leukocyte recruitment and its deficiencies. *Mol Immunol*. 2013; 55:49–58. [PubMed: 23253941]
- Scully C, Hodgson T, Lachmann H. Auto-inflammatory syndromes and oral health. *Oral Dis*. 2008; 14:690–9. [PubMed: 19193198]
- Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. *Cold Spring Harb Perspect Med*. 2011; 1:a006841. [PubMed: 22229120]
- Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, Schellenberg R, Warrington R, Easton D, Anderson D, Hume H. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. *Transfus Med Rev*. 2010; 24(Suppl 1):S28–50. [PubMed: 19962579]
- Shendi HM, Walsh D, Edgar JD. Etanercept and anakinra can prolong febrile episodes in patients with hyperimmunoglobulin D and periodic fever syndrome. *Rheumatol Int*. 2012; 32:249–51. [PubMed: 20020131]
- Shibutani T, Gen K, Shibata M, Horiguchi Y, Kondo N, Iwayama Y. Long-term follow-up of periodontitis in a patient with Chediak-Higashi syndrome. A case report. *J Periodontol*. 2000; 71:1024–8. [PubMed: 10914807]
- Shiffman J. A social explanation for the rise and fall of global health issues. *Bull World Health Organ*. 2009; 87:608–13. [PubMed: 19705011]
- Sigal LH. Basic science for the clinician 58: IgG subclasses. *J Clin Rheumatol*. 2012; 18:316–8. [PubMed: 22955484]
- Silva R, Da Costa JT. Hyper-IgM syndrome—a case report and a clinical perspective. *Eur Ann Allergy Clin Immunol*. 2010; 42:194–6. [PubMed: 21192628]
- Sivolella S, De Biagi M, Sartori MT, Berengo M, Bressan E. Destructive membranous periodontal disease (ligneous gingivitis): a literature review. *J Periodontol*. 2012; 83:465–76. [PubMed: 21859319]

- Small TN, Qasim W, Friedrich W, Chiesa R, Bleesing JJ, Scurlock A, Veys P, Sparber-Sauer M. Alternative donor SCT for the treatment of MHC class II deficiency. *Bone Marrow Transplant.* 2013; 48:226–32. [PubMed: 23000650]
- Sokolic R. Neutropenia in primary immunodeficiency. *Curr Opin Hematol.* 2013; 20:55–65. [PubMed: 23196894]
- Soltesz B, Toth B, Shabashova N, Bondarenko A, Okada S, Cypowyj S, Abhyankar A, Csorba G, Tasko S, Sarkadi AK, Mehes L, Rozsival P, Neumann D, Chernyshova L, Tulassay Z, Puel A, Casanova JL, Sediva A, Litzman J, Marodi L. New and recurrent gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis from Eastern and Central Europe. *J Med Genet.* 2013
- Sparber-Sauer M, Honig M, Schulz AS, zur Stadt U, Schutz C, Debatin KM, Friedrich W. Patients with early relapse of primary hemophagocytic syndromes or with persistent CNS involvement may benefit from immediate hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2009; 44:333–8. [PubMed: 19252534]
- Stein S, Scholz S, Schwaeble J, Sadat MA, Modlich U, Schultze-Strasser S, Diaz M, Chen-Wichmann L, Mueller-Kuller U, Brendel C, Fronza R, Kaufmann KB, Naundorf S, Pech NK, Travers JB, Matute JD, Presson RG Jr, Sandusky GE, Kunkel H, Rudolf E, Dillmann A, von Kalle C, Kuehlcke K, Baum C, Schambach A, Dinauer MC, Schmidt M, Grez M. From Bench to Bedside: Preclinical Evaluation of a SIN gammaretroviral vector for the Gene Therapy of X-linked Chronic Granulomatous Disease. *Hum Gene Ther Clin Dev.* 2013
- Stewart A, Chan Carusone S, To K, Schaefer-McDaniel N, Halman M, Grimes R. Causes of Death in HIV Patients and the Evolution of an AIDS Hospice: 1988–2008. *AIDS Res Treat.* 2012; 2012:390406. [PubMed: 22666562]
- Stiehm ER. The four most common pediatric immunodeficiencies. *J Immunotoxicol.* 2008; 5:227–34. [PubMed: 18569394]
- Stiehm ER. Adverse Effects of Human Immunoglobulin Therapy. *Transfus Med Rev.* 2013
- Stiehm RE. The four most common pediatric immunodeficiencies. *Adv Exp Med Biol.* 2007; 601:15–26. [PubMed: 17712988]
- Stocks RM, Thompson JW, Church JA, Kun S, Simms E. Severe combined immunodeficiency: otolaryngological presentation and management. *Ann Otol Rhinol Laryngol.* 1999; 108:403–7. [PubMed: 10214790]
- Stojanov S, Lapidus S, Chitkara P, Feder H, Salazar JC, Fleisher TA, Brown MR, Edwards KM, Ward MM, Colbert RA, Sun HW, Wood GM, Barham BK, Jones A, Aksentijevich I, Goldbach-Mansky R, Athreya B, Barron KS, Kastner DL. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. *Proc Natl Acad Sci U S A.* 2011; 108:7148–53. [PubMed: 21478439]
- Sulak A, Toth L, Farkas K, Tripolszki K, Fabos B, Kemeny L, Valyi P, Nagy K, Nagy N, Szell M. One mutation, two phenotypes: a single nonsense mutation of the CTSC gene causes two clinically distinct phenotypes. *Clin Exp Dermatol.* 2015
- Sweeney MP, Bagg J, Fell GS, Yip B. The relationship between micronutrient depletion and oral health in geriatrics. *J Oral Pathol Med.* 1994; 23:168–71. [PubMed: 8046654]
- Szczawinska-Poplonyk A, Gerreth K, Breborowicz A, Borysewicz-Lewicka M. Oral manifestations of primary immune deficiencies in children. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2009; 108:e9–20. [PubMed: 19596208]
- Tami-Maury I, Willig J, Vermund S, Jolly P, Aban I, Hill J, Wilson CM. Contemporary profile of oral manifestations of HIV/AIDS and associated risk factors in a Southeastern US clinic. *J Public Health Dent.* 2011a; 71:257–64. [PubMed: 22320283]
- Tami-Maury IM, Willig JH, Jolly PE, Vermund S, Aban I, Hill JD, Wilson CM, Kempf MC. Prevalence, incidence, and recurrence of oral lesions among HIV-infected patients on HAART in Alabama: a two-year longitudinal study. *South Med J.* 2011b; 104:561–6. [PubMed: 21886064]
- Tar I, Kiss C, Marodi L, Marton IJ. Oral and dental conditions of children with selective IgA deficiency. *Pediatr Allergy Immunol.* 2008; 19:33–6. [PubMed: 17651382]
- Tedesco F. Inherited complement deficiencies and bacterial infections. *Vaccine.* 2008; 26(Suppl 8):I3–8. [PubMed: 19388157]

- Tempel TR, Kimball HR, Kakenashi S, Amen CR. Host factors in periodontal disease: periodontal manifestations of Chediak-Higashi Syndrome. *J Periodontal Res.* 1972;26–7. [PubMed: 4272224]
- Thomas DM, Mirowski GW. Nutrition and oral mucosal diseases. *Clin Dermatol.* 2010; 28:426–31. [PubMed: 20620760]
- Tichaczek-Goska D. Deficiencies and excessive human complement system activation in disorders of multifarious etiology. *Adv Clin Exp Med.* 2012; 21:105–14. [PubMed: 23214307]
- Torrelo A, Patel S, Colmenero I, Gurbindo D, Lendinez F, Hernandez A, Lopez-Robledillo JC, Dadban A, Requena L, Paller AS. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. *J Am Acad Dermatol.* 2010; 62:489–95. [PubMed: 20159315]
- Touger-Decker R, Mobley CC, American Dietetic A. Position of the American Dietetic Association: Oral health and nutrition. *J Am Diet Assoc.* 2003; 103:615–25. [PubMed: 12728223]
- Toygar HU, Kircelli C, Firat E, Guzeldemir E. Combined therapy in a patient with Papillon-Lefevre syndrome: a 13-year follow-up. *J Periodontol.* 2007; 78:1819–24. [PubMed: 17760554]
- Tozum TF, Berker E, Ersoy F, Tezcan I, Sanal O. The relationship between periodontal status and peripheral levels of neutrophils in two consanguineous siblings with severe congenital neutropenia: case reports. *Quintessence Int.* 2003; 34:221–6. [PubMed: 12731605]
- Tsai HY, Yu HH, Chien YH, Chu KH, Lau YL, Lee JH, Wang LC, Chiang BL, Yang YH. X-linked hyper-IgM syndrome with CD40LG mutation: Two case reports and literature review in Taiwanese patients. *J Microbiol Immunol Infect.* 2012
- van de Vijver E, van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. *Hematol Oncol Clin North Am.* 2013; 27:101–16, viii. [PubMed: 23351991]
- van der Hilst JC, Frenkel J. Hyperimmunoglobulin D syndrome in childhood. *Curr Rheumatol Rep.* 2010; 12:101–7. [PubMed: 20425018]
- Van Dyke TE, Taubman MA, Ebersole JL, Haffajee AD, Socransky SS, Smith DJ, Genco RJ. The Papillon-Lefevre syndrome: neutrophil dysfunction with severe periodontal disease. *Clin Immunol Immunopathol.* 1984; 31:419–29. [PubMed: 6232030]
- Veerabahu BG, Chandrasekaran S, Alam MN, Krishnan M. Papillon-Lefevre syndrome. *J Oral Maxillofac Pathol.* 2011; 15:352–7. [PubMed: 22144846]
- Verma N, Thaventhiran A, Gathmann B, Party ERW, Thaventhiran J, Grimbacher B. Therapeutic management of primary immunodeficiency in older patients. *Drugs Aging.* 2013; 30:503–12. [PubMed: 23605785]
- Victora CG, de Onis M, Hallal PC, Blossner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. *Pediatrics.* 2010; 125:e473–80. [PubMed: 20156903]
- Visser G, de Jager W, Verhagen LP, Smit GP, Wijburg FA, Prakken BJ, Coffier PJ, Buitenhuis M. Survival, but not maturation, is affected in neutrophil progenitors from GSD-1b patients. *J Inher Metab Dis.* 2012; 35:287–300. [PubMed: 21863279]
- Wald C, Diner H. Dyskeratosis congenita with associated periodontal disease. *Oral Surg Oral Med Oral Pathol.* 1974; 37:736–44. [PubMed: 4524381]
- Walls AW, Soames JV. Dental manifestations of autoimmune hypoparathyroidism. *Oral Surg Oral Med Oral Pathol.* 1993; 75:452–4. [PubMed: 8464608]
- Wang H, Das L, Tan Hung Tiong J, Vasanwala RF, Arkachaisri T. CANDLE syndrome: an extended clinical spectrum. *Rheumatology (Oxford).* 2014; 53:2119–20. [PubMed: 25065002]
- Wang N, Hammarstrom L. IgA deficiency: what is new? *Curr Opin Allergy Clin Immunol.* 2012; 12:602–8. [PubMed: 23026772]
- Ward DM, Shiflett SL, Kaplan J. Chediak-Higashi syndrome: a clinical and molecular view of a rare lysosomal storage disorder. *Curr Mol Med.* 2002; 2:469–77. [PubMed: 12125812]
- Wolf J, Jacobi C, Breer H, Grau A. Chediak-Higashi syndrome. *Nervenarzt.* 2006; 77:148, 150–2, 155–7. [PubMed: 16205875]
- Wolf JE, Ebel LK. Chronic granulomatous disease: report of case and review of the literature. *J Am Dent Assoc.* 1978; 96:292–5. [PubMed: 272415]

- Wu L. The role of monocyte-lineage cells in human immunodeficiency virus persistence: mechanisms and progress. 2011; 6:129–132.
- Wu L, KewalRamani VN. Dendritic-cell interactions with HIV: infection and viral dissemination. *Nat Rev Immunol*. 2006; 6:859–68. [PubMed: 17063186]
- Xia J, Bolyard AA, Rodger E, Stein S, Aprikyan AA, Dale DC, Link DC. Prevalence of mutations in ELANE, GFI1, HAX1, SBDS, WAS and G6PC3 in patients with severe congenital neutropenia. *Br J Haematol*. 2009; 147:535–42. [PubMed: 19775295]
- Yao Q, Furst DE. Autoinflammatory diseases: an update of clinical and genetic aspects. *Rheumatology (Oxford)*. 2008; 47:946–51. [PubMed: 18388145]
- Yashoda-Devi BK, Rakesh N, Devaraju D, Santana N. Leukocyte adhesion deficiency type I—a focus on oral disease in a young child. *Med Oral Patol Oral Cir Bucal*. 2011; 16:e153–7. [PubMed: 21196882]
- Yavuzylmaz E, Yamalik N, Yetgin S, Kansu O. Oral-dental findings in dyskeratosis congenita. *J Oral Pathol Med*. 1992; 21:280–4. [PubMed: 1501159]
- Ye Y, Carlsson G, Wondimu B, Fahlen A, Karlsson-Sjoberg J, Andersson M, Engstrand L, Yucel-Lindberg T, Modeer T, Putsep K. Mutations in the ELANE gene are associated with development of periodontitis in patients with severe congenital neutropenia. *J Clin Immunol*. 2011; 31:936–45. [PubMed: 21796505]
- Yel L. Selective IgA deficiency. *J Clin Immunol*. 2010; 30:10–6. [PubMed: 20101521]
- Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. *Arthritis Res Ther*. 2012; 14:228. [PubMed: 23210525]
- Zimmer J, Andres E, Donato L, Hanau D, Hentges F, de la Salle H. Clinical and immunological aspects of HLA class I deficiency. *QJM*. 2005; 98:719–27. [PubMed: 16087697]
- Zipfel PF, Lauer N, Skerka C. The role of complement in AMD. *Adv Exp Med Biol*. 2010; 703:9–24. [PubMed: 20711704]
- Zumer K, Saksela K, Peterlin BM. The mechanism of tissue-restricted antigen gene expression by AIRE. *J Immunol*. 2013; 190:2479–82. [PubMed: 23456700]

Fig 1.

Overview of the innate and adaptive immune systems. innate immune system lacks memory but can respond quickly to infectious challenges through pattern recognition receptors. Innate immune system includes a humoral arm (complement system, defensins, etc.) and a cellular arm which includes natural killer (NK) cells, and phagocytes (dendritic cells, monocytes/macrophage). Adaptive or acquired immunity is more antigen specific and is our second line of defense involving T cells, and B cells, which express T cell receptors and antibodies, respectively. APCs link the two systems for maximum effectiveness.

Table 1

Nine Categories of Primary Immunodeficiency (IUIS Classification, 2014)

1.	Combined immunodeficiencies
2.	Combined immunodeficiencies with associated or syndromic features
3.	Predominantly antibody deficiencies
4.	Diseases of immune dysregulation
5.	Congenital defects of phagocyte number, function, or both
6.	Defects in innate immunity
7.	Autoinflammatory disorders
8.	Complement deficiencies
9.	Phenocopies of PID

Table 2

Primary Immunodeficiencies

DISEASE	FEATURES	ORAL MANIFESTATIONS
SCID	↓T-, B-cell, Ig response	Candidiasis, viral infections, ulcerative stomatitis
MHC (Class I and II) deficiency	Class I - ↓CD8, Class II - ↓CD4	Oral herpes
DiGeorge Anomaly	↓T-cell, Ig	Enamel hypomineralization, caries, altered eruption patterns
Ataxia-Telangiectasia	↓T-cell, IgA, IgE, IgG	Herpetic gingivostomatitis, candidiasis
Wiskott-Aldrich Syndrome	↓T-cell, IgM	Gingival ulceration/bleeding, palatal petechiae
Hyper IgE Syndromes	↓Th17, normal or ↓B-cell, ↑IgE	Ligneous gingivitis/periodontitis, retained primary teeth, arched palate, recurrent fungal infection
Dyskeratosis Congenita	↓T-, B-cell, Ig	Leukoplakia, early-onset aggressive periodontitis, taurodontism
BTK Deficiency	↓B-cell, all Ig isotypes	Gingivitis, candidiasis, recurrent aphthae
Common Variable IDs	↓IgG + IgA and/or ↓IgM	Necrotizing periodontitis, aphthae, lichenoid lesions, ↑odontogenic infection
CD40 Deficiencies	↓IgG and IgA, normal or ↑IgM	Mucosal ulcerations, ↑infection
Selective IgA Deficiency	↓IgA	Candidiasis, stomatitis, aphthae, herpes labialis, most studies show normal perio condition
Transient Hypogammaglobulinemia of Infancy	↓IgG and IgA	Oral candidiasis
Isolated IgG Subclass Deficiency	↓ one or more of IgG subclasses	↑ susceptibility viral infections in IgG3 deficiency
Chediak-Higashi Syndrome	Nonfunctional lysosomes with impaired degranulation	Early-onset aggressive periodontitis, recurrent ulcers, candidiasis
APECED	Autoimmunity, especially endocrine organs	Chronic candidiasis, enamel hypoplasia
Severe Congenital Neutropenia	↓neutrophils	Severe periodontitis, desquamative gingivitis, ulcers, abscesses, candidiasis
Cyclic Neutropenia	Fluctuating ↓neutrophils	Severe perio disease, aphthous stomatitis
Glycogen Storage Disease Type 1b	Neutrophil and monocyte dysfunction (↓chemotaxis and superoxide production)	Perio disease/overgrown gingiva, ↑bacterial infections, tongue and mucosal ulcers, oral bleeding, epulis, ↑caries
LAD Type 1	Defective leukocyte trafficking	Aggressive perio infections
Papillon-Lefèvre Syndrome (Haim-Munk Syndrome)	Chemotactic defect in neutrophils and monocytes	Early severe destructive perio disease (primary, permanent)
Chronic Granulomatous Disease	↓ killing ability (lack of superoxide production)	Gingival and mucosal ulcerations, gingivitis, periodontitis, ↑ fungal infection
Chronic Mucocutaneous Candidiasis	↓IL-17 production or autoantibodies to IL-17, IL-22	Long-standing multiple mucosal and tongue fungal infection
PFAPA Syndrome	Unknown (probably linked to IL-1 pathway)	Frequent aphthous-like lesions
Familial Mediterranean Fever	IL-1 activation and subsequent inflammation	Frequent oral ulcerations
Hyper IgD Syndrome	Mevalonate kinase deficiency	Oral ulcerations
C3 Deficiency	Loss of complement activation	↑infection with encapsulated microbes
Schimke Syndrome	Mutation SMARCA1 involved in chromatin remodeling	Microdontia, hypodontia, short and thin tooth roots, malformed primary and/or permanent molars
Good Syndrome	↓ one or more isotypes Ig	Lichenoid-like lesions

DISEASE	FEATURES	ORAL MANIFESTATIONS
SAMHD1 Deficiency	↑ CSF alpha-IFN production	Oral ulcerations
Cherubism	Hyperactivated macrophage and ↑ RANKL-induced osteoclastogenesis	Maxillofacial bone degeneration, early loss of teeth, failed eruption of teeth
CANDLE Syndrome	↑ IL-6 production	Severe aggressive periodontitis

Table 3

Relationship of PIDs to Periodontal Conditions

DISORDERS ASSOCIATED WITH PLAQUE-RELATED DISEASE	DISORDERS ASSOCIATED WITH <u>NON</u> -PLAQUE-RELATED DISEASE	DISORDERS NOT ASSOCIATED WITH ANY KNOWN PERIODONTAL CONDITIONS
Wiskott-Aldrich Syndrome	SCID	DiGeorge Anomaly
Hyper IgE Syndrome	MHC (Class I and II) Deficiency	PFAPA Syndrome
Dyskeratosis Congenita	Ataxia-Telangiectasia	Familial Mediterranean Fever
BTK Deficiency	CD40 Deficiencies	Hyper IgD Syndrome
Common Variable IDs	Selective IgA Deficiency	Schimke Syndrome
Chediak-Higashi Syndrome	Transient Hypogammaglobulinemia of Infancy	Cherubism
Severe Congenital Neutropenia	Isolated IgG Subclass Deficiency	
Cyclic Neutropenia	APECED	
Glycogen Storage Disease Type 1b	Chronic Mucocutaneous Candidiasis	
LAD Type 1	Good Syndrome	
Papillon-Lefèvre Syndrome (Haim-Munk Syndrome)	SAMHD1 Deficiency	
Chronic Granulomatous Disease		
C3 Deficiency		
CANDLE Syndrome		