THE DENTAL CLINICS OF NORTH AMERICA

Dent Clin N Am 47 (2003) 709–731

Immune suppression and considerations for dental care

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The term ''immunocompromised'' is used to describe people who are not capable of mounting an effective immune response. These individuals are at an increased risk for infections as a consequence of inherent or acquired abnormality of their immune system. Immunocompromised individuals include those affected by and treated for cancer, bone marrow suppression, immunosuppressive therapy, HIV, and other congenital or acquired conditions, or states in which the immune defense is altered. As a result of increasing knowledge of the intricacies of the immune system, the term immunocompromised patient has evolved to encompass new meaning and relevance. A growing number of patients are living with iatrogenic-deficient immune systems due to advancement of medical technology and the ability of medications to modulate functions of the immune response. To the clinician, this means facing a new challenge of treating a population at greater risk for infection and other associated complications. Although, it is often possible to prevent or manage infections with prophylactic medications and ongoing therapeutic interventions, exposure to particular pathogens and consequent dissemination could potentially be life threatening for the immunocompromised patient.

To manage and treat an immune-deficient individual safely and effectively, it is important for the dental clinician to: (1) be able to identify which patient is immunocompromised, (2) be able to determine the type of immune deficiency, and (3) have a basic understanding of the immune system and how specific dysfunctions increase the risk of infections and complications. This article will address these three issues by reviewing the

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doi:10.1016/S0011-8532(03)00038-7

various components of the host defense that, when altered or missing, lead to a compromised immune system and by discussing opportunistic infections and complications that may occur within this framework. Dental considerations for the immune-deficient patient also will be addressed.

Role of the immune system

The immune system is an intricate network of specialized cells and organs each with specific roles and modes of communication. When functioning properly, the host defense is able to fight off infections mounted by numerous agents including bacteria, fungi, viruses, and parasites and to control abnormal cell growth, which may lead to different neoplasms.

One of the initial steps in the immune response is the recognition by host cells of the immunogenic epitopes on foreign materials. The processes that follow include initiation of various mechanisms resulting in an inflammatory response leading to inflammation, destruction of microbial agents, and destruction of foreign toxic compounds [1].

Cellular and humoral responses occur through specific molecular interactions, setting off cascades of molecular events. In immunocompetent states, immunologic events are regulated by interactions between antibody-forming cells, helper and suppressor cell pathways, cytokine mediation, or through specific immunologic tolerance [2]. The ability of the system to function properly relies on this dynamic network's ability to regulate and communicate effectively. The result is a balanced system that produces a prompt, appropriate, and effective response to foreign pathogens. Abnormal regulation or incompetence of the immune system may prevent the host from properly handling antigenic stimuli, resulting in a state of immune deficiency. Immune dysfunction may also cause immune deficiency, but can also promote the development of autoimmune diseases where the host reacts to its own tissues [3].

Multiple levels of organization exist within the immune system, including genes, cells, and mediators. Any qualitative or quantitative change in the system may produce profound effects, leaving the host susceptible to opportunistic infections, and immune dysregulation leading to an altered immune response [1].

Disorders affecting the host defense

Certain immune deficiencies may predispose an individual to infection by particular pathogens that would normally be eradicated by that specific host defense mechanism [4]. Table 1 summarizes possible defects in the host defense system and the pathogens associated with the deficiency. The type and severity of infection are often unpredictable, and a wide spectrum of infections may be encountered in immunocompromised patients [5].

Table 1
Defects in host defense and typical pathogens associated with the deficiency

Host defense Impairment	Bacteria	Fungi	Virus	Parasite
Neutropenia	*Staphylococcus aureus* Coagulaseegative *staphylococcus spp,* *Viridans streptococci* *Clostridium spp.* *Bacteroides spp.* *Pseudomonas eruginosa*	*Candida* species (*C. albicans, C. tropicalis, C. krusei*) Aspergillus species *Mucor, Trichosporon*		
Impaired cellular immunity	*Legionella* *Nocardia asteroids* *Mycobacteria tuberculosis* Atypical mycobacteria	*Cryptococcus neoformans* *Histoplasma capsulatum* *Candida* *Aspergillus spp.*	Varicella-zoster virus Herpes simplex virus Cytomegalovirus Epstein Barr virus Human Herpesvirus 6 Human papillomavirus	*Pneumocystic carinii* *Toxoplasma gondii*
Immunoglobulin abnormalities	*Streptococcus pneumoniae* *Staphylococcus aureus* *Haemophilus influenzae*		Enteroviruses	Giardia
Complement deficiencies	*S pneumonia* *H influenzae* *Neisseria spp.*			
Compromised physical barrier (oral mucositis)	*Viridans streptococci* *Enterococcus* spp. (*peptococcus, peptostreptococcus*)	*Candida* spp.		
Splenectomy	*S pneumoniae* *Capnocytophaga* *H influenzae*			Babesia

However, it is still important to have a basic understanding of the underlying immune defect to help elucidate the reason for predisposition to a particular infection. Additionally, management strategies may differ based upon the underlying immunologic defect.

On a most basic level, quantitative or qualitative defects of neutrophils or other phagocytic cells predispose individuals mainly to bacterial infections. Absent or defective functional T-lymphocytes make the host more susceptible to fungal, viral, and parasitic infections and diminishes control over neoplastic growth [3].

Various states of immune suppression may result from primary congenital defects, or more commonly, may be acquired from a secondary source, such as HIV infection or drug therapy. To complicate matters further, in many conditions there is a combination of deficiencies. These deficiencies may occur as a result of congenital or acquired defects in the phagocytic system, the humoral system, the cell-mediated system, or the complement system.

Primary immune deficiencies

Individuals born with a faulty immune defense system may have clinical manifestations of primary immunodeficiency (PI) disease. Because a broad spectrum of defects may occur in the immune system, some individuals may have severe forms of disease, whereas others may have few or no symptoms. As a result of this variation in clinical presentations, individuals affected by a PI may not be assigned an appropriate disease entity. According to the National Institute of Allergy and Infectious Diseases (NIAID), PIs affect nearly 500,000 people in the United States [6]. The incidence of PIs, exclusive of asymptomatic IgA deficiency and mannose binding lectin (MBL), is estimated to be approximately 1 in 5000 live births [7].

Immune deficiencies can result from primary defects in hematopoietic stem cells, phagocytic cells, T cells, B cells, or complement. These immune defects affect a particular branch or portion of the immune system that is primarily involved. Table 2 categorizes PI disorders based on the host immune system. Phagocytic defects can cause primary immune deficiencies such as neutropenia, adhesion defects, signaling defects, or intracellular killing defects. Combined humoral and cell-mediated deficiencies are the most serious type of immune disorders. Infections occur early on in life, and the prognosis is poor unless therapeutic intervention is instituted to reconstitute the defective immune system.

The most common immune deficiency, affecting an estimated 1 in 600 births, is the absence of secretory IgA, or selective IgA deficiency [8]. This lack of IgA is caused by a defect in B-lymphocytes where IgA-bearing cells fail to mature into IgA-secreting plasma cells. Individuals with this deficiency are often healthy, leading normal lives. However, many who have symptoms typically have recurrent infections and an increased

Table 2
Primary immune-deficiency disorders

Category	Disease	Mechanism	Clinical manifestations
Phagocytic deficiencies	Cyclic neutropenia	Mutation in ELA2	Increased infection risk, aphthous ulcers, gingivitis, stomatitis, cellulitis
	Congenital neutropenia		Severe neutropenia, recurrent bacterial infections, lack of promyelocyte maturation
	Congenital agranulocytosis	Decreased G-CSF production	Decreased neutrophil count
	Leukocyte-adhesion deficiency	Defective synthesis of in the beta chain of integrin's adhesion molecule	Recurrent bacterial infections with no pus formation
	Chronic granulomatous disease	Decreased peroxide production 2° to defective NADPH oxidase leading to defective phagocytosis	Recurrent bacterial and fungal infections
Humoral deficiencies	X-linked agammaglobulinemia	Mutation in gene coding for tyrosine kinase leading to total absence or deficiency of serum Igs	Chronic enteroviral infections and chronic pulmonary disease
	X-linked hyper-IgM syndrome	Decrease serum IgG, IgA, and IgE	Recurrent bacterial infections of the sinopulmonary and gastrointestinal tracts, and hypertrophy of lymphoid tissues
Cell mediated deficiencies	DiGeorge syndrome	Deletion of chromosome 22q11	Thymic aplasia, cardiovascular malformations, dysmorphic facial features
Complement deficiencies	Deficiency of C1 inhibitor	Dysregulation of the classical pathway involving C4 and C2	Hereditary angioedema
	C3 deficiency	Lack of activation of C5 and formation of membrane-attack complex	Immune complex disease Susceptible to recurrent bacterial infections
Combined immunodeficiencies	Common variable immunodeficiency	Several mechanisms are proposed	Recurrent bacterial infections, decreased serum Ig, abnormal antibody response
	Severe combined immunodeficiency disease	Dysfunction of the common gamma chain leading to disruption in B and T cell differention and proliferation	Severe opportunistic infections, chronic diarrhea, failure to thrive.
	Wiskott-Aldrich syndrome	Defect in gene coding the WAS protein	Thrombocytopenia, eczema, combined immunodeficiency

frequency of autoimmune disorders including arthritis, lupus, autoimmune endocrinopathies, ulcerative colitis, Crohn's disease, and autoimmune hematologic disorders. There is no specific treatment for IgA deficiency; however, bacterial infections are managed with antibiotics.

Another PI that occurs relatively frequently is common variable immunodeficiency disease (CVID). This is a heterogenous group of disorders that involves both B-cell and T-cell function, which manifests predominantly as hypogammaglobulinemia [9]. The presentation of this deficiency is truly variable. Although it may present in infancy, it varies in the age at presentation. CVID is characterized by a decrease in serum Ig levels, an abnormal antibody response, and recurrent bacterial infections. Also, autoimmune disorders and a higher incidence of malignancy are associated with CVID. Individuals with moderate or severe CVID may receive intravenous immunoglobulin every 3 to 4 weeks to restore normal antibody levels. Bacterial infections are managed as needed.

Among the rarest form of PIs is severe combined immunodeficiency disease (SCID), which is caused by a genetic abnormality leading to either a lack of the essential enzyme adenosine deaminase or an inability to produce interleukin (IL)-2 receptor gamma chain. Whereas most PIs are due to molecular defects that are mostly recessive traits, some are caused by mutations in genes on the X chromosome. In either case, SCID is an inherited disorder affecting 1 in 100,000 individuals [10]. Both the humoral and the cellular immune function are affected in SCID, where clinical symptoms may be evident in the first few months of life. Infections are usually serious or even life-threatening. Infants commonly have chronic skin infections, candidiasis of the oral cavity and diaper area, chronic hepatitis, gastrointestinal complications, and blood disorders. Individuals are typically treated with hematopoietic stem cell transplants or with specific enzyme replacement therapy.

Complement deficiencies are extremely rare, accounting for 1% of all PIs [7]. Similar to other PIs, this type of deficiency usually does not present until adulthood. Typically, a genetic deficiency in the complement system may impair the immune defense; however, the consequence of a particular defect depends on which complement component is deficient. Deficiencies in the early classic pathways result in more severe clinical presentations such as an increase in immune-complex diseases such as systemic lupus erythematosus and vasculitis and an increased susceptibility to recurrent bacterial infections. Hereditary angioedema, which is associated with localized edema of oral mucosa or subcutaneous tissue and bowel or upper respiratory tract, is caused by deficiency of C1 inhibitor, which regulates the activation of the classic pathway [11]. Other less severe complement deficiencies have more subtle clinical presentations due to compensation by the alternative pathway [12]. Although there is no specific therapy for complement deficiencies, current research is exploring the use of complement concentrates to replace deficient components.

More than 80 types of PIs are recognized today, all with one thing in common: increased susceptibility to infection, the hallmark of PIs. As has been mentioned, infections are not the only complications these individuals may face; some PIs are associated with other disorders of the immune system such as arthritis, autoimmune diseases, allergic diseases or may involve one or several organ systems [13]. A higher incidence of malignancies in these individuals is also found.

In the past, PIs had severe and life-threatening consequences; however, mortality rates have improved significantly due to hematopoietic stem cell transplantation and replacement therapy. As specific genetic defects are elucidated, gene therapy may provide promising alternative therapy in the future.

When evaluating a patient who is suspected of having an immune deficiency, it is important to know that an individual with a normal immune system will have a respiratory infection on an average of six to eight times per year in the first 10 years of life, an average of six episodes of otitis, and two bouts of gastroenteritis per year during the first 2 to 3 years of life [12]. In contrast, patients with an impaired immune system tend to have higher recurrences of infection that are more severe, longer, and respond less well to conventional therapies.

To render safe dental treatment, clinicians must identify individuals with immune impairment and recognize which components of the patient's immune defense may be compromised. With this knowledge, appropriate preventative measures can be taken, including minimizing infections through proper and timely dental care, as well as prophylaxis with suitable medications.

Acquired immune deficiencies

The immune defense system may be affected to varying degrees by both therapeutic interventions and underlying diseases. The advent of aggressive treatment methods for many illnesses has altered the classic concept of specific defects of host defense mechanisms in the various types of diseases. In most cases, the effects of chemotherapy and radiation therapy are the primary factors in determining the nature and depth of the immune defect [14]. Box 1 lists the causes of immunodeficiency.

Acquired immunodeficiency is more common than primary deficiencies of the immune system. As with PIs, the dental clinician should be aware which conditions or medications may affect the immune response. Among other disease specific complications and effects from various treatment modalities, these individuals are largely at risk of localized and disseminated infection. Recognition of the presence of an immune defect is only the first step. The next level of care is to understand what complications may arise from each condition and state of immunosuppression. The following is an overview of various states of acquired immunodeficiency resulting from existing condition, or treatment modalities.

Box 1. Causes of immunodeficiency

Neutrophil defects—quantitative and qualitative
Leukemia and myelodysplastic syndromes
Nonmalignant hematologic diseases
Malignancies
HCT recipients
Solid organ transplant recipients
Poorly controlled diabetics
HIV disease
Congenital immune deficiency disorders
Radiotherapy
Pharmacologic agents:
- chemotherapy
- corticosteriods—long-term
- immune modulating drugs

Splenectomy and splenic dysfunction

Neutropenia

Neutropenia is defined as an absolute blood neutrophil count that is more than two standard deviations below the normal mean [15]. Neutrophil counts vary with both age and race. For a white adult, an absolute neutrophil count <1500 cells per μL is considered neutropenia. For an African American, the lower limit of a normal neutrophil count is 1200 cells per μL. In general, mild neutropenia is 1000 to 1500 cells per μL, moderate neutropenia is between 500 and 1000 cells per μL, and severe neutropenia is <500 cells per μL. Although individuals with severe neutropenia have the highest risk for life-threatening infections, this stratification is helpful in predicting the risk for infection in most neutropenic patients [15].

Quantitative deficiencies of neutrophils usually occur secondary to acquired immune defects but may also be seen in congenital phagocytic deficiencies. In acquired deficiencies, neutrophils are the cells most often affected by the immune impairment. In healthy individuals, precursor cells divide rapidly within the bone marrow to maintain homeostatic levels. Precursor cells and immature neutrophils are both affected by drugs that target rapidly dividing cells. Consequently, neutrophils are affected by chemotherapeutic agents, radiation, and other cytotoxic agents.

Neutropenia and reduction of other white blood cells occur after treatment with cytotoxic drugs because of the deleterious effect on the proliferation of normal hematopoietic progenitor cells. Therapeutic radiation can also cause neutropenia based on the dose rate and amount and the area of the body being irradiated. Total body irradiation, given before hematopoietic stem cell transplants, is an example of the negative

impact of irradiation. Therefore, profound neutropenia should be expected during treatment of certain malignancies. It may persist for 3 to 4 weeks, and in some cases possibly longer. In iatrogenic granulocytopenia, existing granulocytes may not be able to function normally as chemotherapy and irradiation also interfere with peripheral cells. This may result in decreased chemotaxis, diminished phagocytic capacity, and defective killing by granulocytes [14].

Treatment-related neutropenia is one of the most important primary risk factors for infection [4]. The classic study by Bodey and colleagues [16] characterized the relationship between granulocytopenia and serious infection. The group demonstrated that the risk of infection increases significantly when total granulocyte count decreases <1000 cells per μL and is most significant when the counts drop <100 cells per μL.

Individuals with absolute neutrophil counts of <500 cells per μL are at a greater risk of infections from endogenous flora and colonization by various nosocomial organisms. This is particularly significant in patients with neutropenia caused by acquired disorders of production, such as those receiving cytotoxic therapy, immunosuppressive drugs, or irradiation, because of the overall compromised status of the immune system [15].

Immune-mediated neutropenia may also occur in association with autoimmune diseases such systemic lupus erythematosus (SLE), various connective tissue diseases, or immune thrombocytopenic purpura [15]. Autoantibodies may cause destruction of neutrophils via complement-mediated lysis or splenic phagocytosis of opsonized neutrophils [17]. Neutropenia also occurs in hematologic malignancies, lymphoma, and solid tumors and may be associated with lymphoproliferative neutropenia.

Congenital causes of neutropenia also may lead to immune dysfunction. Cyclic neutropenia is a rare autosomal dominant disorder, which is characterized by regular, periodic oscillations in the number of peripheral neutrophis from normal to neutropenic values. This recurrent neutropenia usually lasts from 3 to 6 days over a 21-day period [18]. Patients affected by cyclic neutropenia are often asymptomatic but may develop aphthous ulcers, gingivitis, stomatitis, and cellulitis during periods of severe neutropenia [19]. Death from severe infection occurs in $\sim$10% of individuals [20]. The cause of this congenital neutropenia has been identified as a mutation in the neutrophil elastase gene (ELA2). However, the exact association of how the elastase enzyme affects cyclic neutrophilic changes has yet to be determined [18].

Severe congenital neutropenia, also called Kostmann's syndrome, is another rare form of neutropenia characterized by onset during infancy and recurrent severe pyogenic infections, including cellulitis, perirectal abcesses, peritonitis, stomatitis, and meningitis [19]. Platelet counts are normal but anemia associated with chronic inflammatory disease is common. These individuals usually respond well to granulocyte colony-stimulating factor or filgastim, which has improved the mortality rate [18]. Otherwise, with supportive care alone, most individuals do not survive adolescence [15].

Phagocytic dysfunction

Phagocytes are an integral part of the body's defense system. In particular, polymorphonuclear leukocytes, or neutrophils and monocytes, are two of the most important components of the cellular host defense against invasive bacteria and fungi [4]. Both quantitative and qualitative phagocytic defects may result in immune defects. This part of the immune system is particularly involved in the process of ingesting and killing microorganisms. Phagocytes must be able to adhere to vascular endothelial cells, emigrate across the endothelium, react at the site of inflammation, and attach to the microorganism, to phagocytize, kill, and digest the offender. Consequently, there are numerous steps at which a defect can occur.

Neutropenia, a quantitative phagocytic defect, has been discussed earlier. Primary disorders of phagocytic function include chronic granulomatous disease and myeloperoxidase deficiency. The former is characterized by defective oxidative metabolism of phagocytes, whereas the latter is one of the more common granulocyte disorders [18]. Defects of phagocytes also occur as a result of iatrogenic causes by the administration of phamacologic agents or by radiation.

Neutrophil dysfunction occurs in many acquired conditions, including poorly controlled diabetes and malnutrition. It is likely that these patients will frequently be encountered in a dental practice. In poorly controlled diabetes mellitus, patients are prone to vascular disease, neuropathy, and suffer from poor wound healing and associated infections. Poor wound healing can be explained by aberrations such as impaired opsonization and decreased chemotactic activity of granulocytes and monocytes [21]. Because of the impaired function of neutrophils in patients with hyperglycemia, correcting the imbalance may improve the phagocytic function of neutrophils and prevent other diabetes-associated complications [22].

Infection

Various infections, particularly viral, may impair cell-mediated immunity either through direct effect on key cellular components, such as T lymphocytes and macrophages, or indirectly by affecting other mechanisms of immune regulation [23]. Human immunodeficiency virus (HIV-1, HIV-2) is the most notable viral infection associated with impaired cell-mediated immunity. The virus primarily infects lymphoid tissue, leading to profound immune suppression due to the loss of CD4(+) T-helper cells. Individuals gradually develop more profound immunosuppression, predisposing them to severe fungal, viral, and protozoal infections, as well as various neoplasms, which may present in the oral cavity. The prevalence and incidence of oral lesions are significantly affected by the immune system and are directly associated with immune deficiency and HIV disease progression [24] (see also article by Cleveland and Cardo in this issue).

Other viral infections also can cause defects in cell-mediated immunity. These organisms include cytomegalovirus, Epstein-Barr virus, hepatitis B virus, and influenza [4]. In vivo studies have shown that other nonviral infections such as tuberculosis and syphilis may be associated with impaired cell-mediated defenses [25,26].

A type of disseminated or systemic infection is sepsis, a poorly understood phenomenon which is the leading cause of death among critically ill patients in the United States, causing more than 200,000 deaths annually [27]. It has been defined as a "systemic inflammatory response syndrome" that occurs during an infection [28]. The prevailing theories in the pathogenesis of sepsis include the consensus that there is some level of immune dysfunction, which occurs in the presence of disseminated infection [29]. Oral infections have been shown to be a significant source of infection [30].

Some features found in patients with sepsis are consistent with immunosuppression: inability to resolve an infection, a loss of delayed hypersensitivity, and a predisposition to nosocomial infections [31]. Elucidation of the immune response to pathogens has led to some understanding of the immune dysfunction that occurs during sepsis. Although the true mechanism of organ failure and death from sepsis is not known, manipulation of an individual's immune response may be part of future therapy for sepsis.

Malignant disorders and myelodysplasia

Cancer continues to be one of the most common diseases in the United States. One out of four deaths in the United States is due to cancer. In 1999, it was estimated that by the year 2002, more than 1.2 million Americans would receive a new diagnosis of cancer and that over 555,500 deaths would occur from cancer [32]. Malignant disorders impart damage on various organ systems depending on the type of malignancy or disease. The host defense is one system that may be affected.

Although chemotherapy and radiation therapy are significant factors in the impairment of host defense in individuals affected with cancer, patterns of infection may also be influenced by other disease related abnormalities. Granulocytopenia is most commonly associated with hematologic malignancies, lymphomas, and the treatment of solid tumors with cytotoxic therapy. Bone marrow failure, which occurs in several hematologic disorders, leads to neutropenia, a major risk of infection. In addition, patterns of infection may vary in certain conditions like acute myelogenous leukemia and aplastic anemia due to the course of the disease or various treatment regimens [4].

A patient's underlying disease is important in determining the risk of infection. Individuals with blood dyscrasias have been shown to have increasing frequency and severity of infection with gradual increases in severity and duration of granulocytopenia [33]. In one study, investigators

showed that approximately one third of individuals with acute leukemia or chronic leukemia in the blast phase had oral infections [34]. Another investigation demonstrated that ~10% of patients receiving chemotherapy for solid tumors developed oral infections, mostly of fungal origin [35]. Oral infections that occur during cancer therapy continue to be a concern for health care providers. Several published guidelines describe pretreatment strategies for oral health that are directed at preventing oral infections [36–39].

Functional defects in the immune defense should also be considered in malignant disorders and myelodysplasia. Significant functional impairment of mature neutrophils has been documented in patients with chronic myelogenous leukemia and myelodysplasic syndromes [40]. In addition, phagocytic dysfunction has been noted in patients with chronic lymphocytic leukemia and multiple myeloma.

Humoral impairment also occurs in malignant disorders. In multiple myeloma, a malignant proliferation of plasma cells, humoral impairment appears to be related to disease stage. This has been shown to be caused by the synthesis of a protein that is induced by malignant plasma cells and selectively suppresses B-cell function [41]. Also, individuals with B-cell chronic lymphocytic leukemia appear to have irregular immunoglobulin chain synthesis resulting in hypogammaglobulinemia [42,43]. Patients affected by these disorders are the most susceptible to recurrent infections from encapsulated bacteria such as *S Pneumoniae* or *H Influenzae*.

Transplant

Both solid organ transplantation and hematopoietic cell transplant (HCT) have become lifesaving therapeutic options for several conditions. In 2000, the United Network for Organ Sharing reported 22,965 solid organ transplants [44]. Today, with even more transplants performed, the 5-year survival rate for single solid organ transplant is >80% for kidney, pancreas, and liver [44]. This can be attributed to advances in surgical techniques, organ preservation, and improved postoperative care, including factors that reduce infection rates [45]. Despite these advances, life-threatening infections are still a serious complication of transplantation. Oral infection associated with septicemia was reported in 35% of leukemia and transplant patients [46].

Many complex mechanisms are associated with the immune status of a transplant recipient. The state of immune suppression in these individuals is determined by several factors including the presence of underlying diseases, postoperative metabolic factors, and concurrent infection with immunomodulatory viruses such as cytomegalovirus, Epstein-Barr, and HIV [47]. Another major consideration in the determination of immune competence in these patients is the immunosuppressive regimen. The type of medication, dosage, and duration of therapy are all critical factors and influence the immune status.

Infections are a common complication of both solid organ transplant and HCT. In solid organ transplantation, abnormality in cellular immunity occurs as a result of immunosuppressive therapy. Among transplant recipients, those who receive renal transplants have a lower occurrence of infections than individuals with heart or lung transplants [48,49]. In general, infections follow a predictable pattern in the posttransplantation period. This time period has been divided into three phases: the first month posttransplant, 1 to 6 months posttransplant, and 6 months and beyond [47].

During the 1-month posttransplant period, infections are similar to those in immunocompetent postoperative patients [45]. Organisms causing infection are commonly endogenous flora from the gastrointestinal tract, including *Candida* species and other hospital-acquired bacteria. The only significant viral infection during this early posttransplant phase is recurrent herpes simplex virus (HSV); however, the incidence has decreased dramatically with the use of prophylactic antiviral medications. Tissue ischemia may also contribute to the risk of infection during early phases of posttransplant.

After the first month and up to 6 months posttransplant, solid organ transplant recipients have maximum dysfunction of cellular immunity. Infections that occur usually are intracellular or opportunistic pathogens including cytomegalovirus, herpes simplex virus 6 (HHV-6), *Pneumocystis carinii*, and *Cryptococcus neoformans*. Cytomegalovirus typically is the cause of many posttransplant febrile episodes and may depress immune function further [49]. Oral candidiasis and recurrent intraoral herpetic stomatitis also frequently occur during this period.

The third phase after transplantation is 6 months and beyond the transplant surgery. The risk of infection is variable and depends on the posttransplant course during the first two phases and the state of immunosuppression for each individual. Those individuals with recurrent or chronic infections during the first two phases have a higher risk of infection. Also, immunosuppressive agents given at a higher dose increases the risk of infection by *Pneumocystis carinii*, *Cyptococcus neoformans*, and *Aspergillus* spp. For transplant recipients on lower immunosuppressive doses, the risk of community acquired infection with pneumococci and influenza is still a concern [49].

Since the 1960s, allogeneic and autologous HCT have evolved into an increasingly successful therapy for several underlying diseases. Currently there are more than 20,000 patients in the United States who have survived for over 5 years after transplantation [50]. With the tremendous growth of HCT, this number is expected to increase even further. Although these figures are encouraging, the posttransplant period for HCTs is fraught with complications.

Among the complications of HCT is the increased susceptibility to infection. In addition, long-term immunosuppressive therapy can diminish the inflammatory response and attenuated signs and symptoms of infection.

Complete immunologic reconstitution may take 2 years or longer, even in the absence of immunosuppressive therapy [50]. Delays in immune recovery can occur with the presence of chronic graft-versus-host disease (GvHD). Although immunologic function may recover more rapidly in autologous HCT, prolonged immunosuppression occurs in both, increasing the susceptibility of infection [51].

During the immediate period after HCT, the primary defects in the immune defense are granulocytopenia, the loss of mucosal barrier integrity, and placement of central venous catheters or lines [52]. Prolonged neutropenia and breaks in mucocutaneous barriers due to intensive conditioning regimens and frequent vascular access for patient care are respectively critical risks for the development of infection. The most common infection during this period of profound neutropenia and lymphopenia is usually from a bacterial source, but endogenous fungal flora such as *Candida* spp. or inhalation of mold spores like *Aspergillus* spp. may cause opportunistic fungal infections. This pre-engraftment phase ends approximately 30 days after HCT, around the time of recovery from neutropenia.

After the recovery of neutropenia, the postengraftment phase continues up to 100 days after HCT. During this time of cell recovery, defects in both cell-mediated and humoral immunity predominate [53]. Herpes viruses, such as cytomegalovirus, may be reactivated causing pneumonia, hepatitis, and colitis and may potentiate superinfection with opportunistic pathogens [39]. Reactivation of oral HSV may lead to stomatitis or painful oral lesions. Other dominant pathogens during this phase include *Pneumocystis carinii* and *Aspergillus*, particularly in those individuals with GvHD. As in solid organ transplants, the risk of infections with these pathogens continues for as long as individuals remain on immunosuppressive therapy.

The late phase, or late posttransplantation period, begins after day 100 and ends upon the discontinuation of immunosuppressive medication. Dysfunction of cellular and humoral immunity may continue, leading to infections with varicella zoster virus, encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, and invasive aspergillosis [54]. The most common clinical infections during this phase include sinusitis, bronchitis, pneumonia, and otitis media [52]. Chronic oral candidiasis can also develop during the late posttransplant phase. Overall, individuals with organ rejection, or GvHD, and who are on intensive immunosuppressive therapy have higher risks for infections.

With the growing number of successful transplants, oral health care providers are more likely to encounter transplant recipients as dental patients. Aside from increased risk of various infections, these patients typically take multiple medications. Cyclosporine, tacrolimus, corticosteroids, azathioprine, and mycophenolate mofetil are among the most commonly used immunosuppressive drugs [55]. These individuals also may be on prophylactic medications. The oral health care provider should be aware of the interactions and side effects of immunosuppressive therapies.

For instance, over the years, cyclosporin has long been associated with gingival overgrowth [56–58]. Cyclosporin also has potential drug interactions with rifampin, isoniazid, nafcillin, macrolides, azole agents, and fluoroquinilones. Consequently, caution must be used when administering fluconazole, quinolones, and other antibiotics.

Aspects of oral health care for the immunocompromised host

There are several important aspects that need to be addressed when treating an immunocompromised patient. First, host integrity is of utmost importance when considering a patient's susceptibility to infection. Oral pathogens are more likely to cause local destruction, bacteremia, or septicemia when the integrity of the mucosa is compromised. Secondly, these individuals are more likely to develop oral or systemic opportunistic infections because of their immune system's inability to suppress and destroy pathogens. Also, oral lesions may develop as a result of immunosuppressive therapy. The next aspect in the clinical approach to these individuals should include a comprehensive understanding of the side effects and drug interactions resulting from medications or immunosuppressive therapies the patient may be taking. Finally, the clinician should consider how each immunocompromised patient will respond to conventional oral health care. This will depend upon the individual's immune status at the time treatment is rendered. The oral health care provider, in consultation with the patient's physicians, should be able to decide on the appropriate time and modifications for dental treatment to minimize the potential for adverse events. This section addresses each of these aspects of the oral health care provider's approach to treating an immunocompromised patient.

Host integrity

The oral health of immunocompromised individuals is particularly of concern because oral pathogens have been shown to affect the integrity of the host by causing bacteremia and septicemia [59]. Although common daily events such as toothbrushing, flossing, and chewing may cause bacteremia, dissemination of bacteria from the oral cavity into the bloodstream is a great concern for dentists during invasive dental procedures, such as extractions, scaling, and root planing. It is imperative to understand that the type and degree of bacteremia differ and are related to the immediate condition of the oral cavity in terms of amount of plaque, presence of gingival inflammation, or size of periapical lesion. With more than 350 bacterial species identified from dental plaque and >150 bacterial strains isolated from endodontic infections, oral flora typically do not pose a significant risk to healthy individuals [60]. Yet, to the immunocompromised individual, oral bacterial infections could potentially be life threatening. The exact morbidity and mortality rates associated with oral infection in immunocompromised

individuals are difficult to determine as the source of infection and type of pathogen may not always be isolated.

Risk of infection from exogenous pathogens

Various published protocols outline established procedures, which diminish the exposure to exogenous pathogens in the dental setting. The practice of standard precautions is generally accepted as a standardized approach to infection control in the medical and dental environment. (see also article by Eklund in this issue). There are no specific guidelines for the treatment of immunocompromised individuals beyond the standard precautions. However, there is growing concern regarding the preponderance of scientific evidence of heavy contamination of dental water lines with various micro-organisms including *Legionaella pneumonophilia*, the agent responsible for legionnaires' disease, *Pseudomonas aeruginosa*, and non-tubercular mycobacterium species [61] (see also article by Eklund in this issue). Keeping water from dental unit waterlines to <500 colony-forming units per mL and using only sterile water during all surgical procedures is thought to diminish adverse events associated with biofilm [62].

There is sufficient evidence that dental personnel and patients are being exposed to potential pathogens and resistant micro-organisms found in the biofilm of dental unit water lines [63,64] (see also article by Eklund in this issue).

Although infections from these exogenous sources have never been documented among immunosuppressed dental patients, disease transmission associated with biofilm formation is reported in other health care settings [65,66].

Susceptibility to infection from indigenous microbes

The pattern of microbial colonization is typically altered in the state of immune suppression. The oral flora may include both commensal and acquired micro-organisms, which could cause severe and life-threatening infections. During chemotherapy, shifts occur in the oral flora from predominantly gram-positive flora to predominantly gram-negative micro-organisms and increase opportunistic fungal infections, particularly *Candida* spp [67]. In a state of immune suppression, oral pathogens such as *Viridans streptococci* have an increased pathogenicity, whereas in healthy individuals, these gram-positive cocci have a low degree of virulence [68]. Many studies implicate oral flora as a significant cause of increased morbidity and mortality in immunosuppressed individuals [60].

One investigation of 57 patients in a medical ICU evaluated the relationship between dental plaque colonization during the hospital stay and the development of nosocomial infections, including pneumonia and bacteremia. The authors found that the colonization by aerobic pathogens in dental plaque was a likely source of these infections [69]. Due to difficulties in oral hygiene, changes in salivary composition, and alteration

of the oral flora due to antimicrobial therapy, immunocompromised patients may also be at a higher risk of dental plaque colonization.

Hence, it has become an acceptable practice to reduce prophylactically the oral foci of infection to minimize systemic complications caused by oral infection particularly in neutropenic patients and in those treated with chemotherapy [70,71]. This can be achieved by using appropriate therapy upon recognition of an oral infection and is most effective when preventative strategies are used. Proper dental treatment planning may help prevent future life-threatening infections in these groups of patients. Indigenous oral flora can also be reduced before dental treatment by giving an antibacterial rinse such as chlorhexidine to prevent and avoid potential complications [72,73].

Opportunistic infections

For oral health care providers, the focus of concern is the mouth. The oral cavity is a common site of infection and disease for the immunocompromised individual [74]. Table 3 lists the potential infections that may be encountered in the oral cavity of an immunocompromised individual. Although the same types of lesions are commonly found among many types of immunocompromised patients, the underlying cause of immune suppression often varies [75,76]. Overall, the dentist should take a proactive role in the detection and prevention of complications from oral opportunistic infections in this group of patients.

Table 3
Infections of the oral cavity of immunocompromised individuals

	Organisms	Oral manifestations
Fungal	Candidiasis	Pseudomembranous, erythematous, hyperplastic candidiasis, and angular cheilitis
	Aspergillosis	Yellow or black necrotic ulcers
	Cryptococcosis	Solitary chronic ulcerations or nonhealing extraction wounds
	Histoplasmosis	
	Coccidioidomycosis	
	Blastomycosis	
Viral	Herpes simplex	Severe and atypical gingivostomatitis, recurrent herpetic stomatitis
	Varicella Zoster virus	Unilateral, multiple vesicular lesions or ulcers
	Cytomegalovirus	Chronic painful ulcers
	Epstein-Barr virus	Oral hairy leukoplakia, mononucleosis
	Human herpes virus 8	Kaposi's sarcoma
	Human papillomavirus	Oral warts, papillomas, focal epithelial hyperplasia
Bacterial	Gram positive, gram negative, anaerobes	Destructive gingival and periodontal infections including necrotizing ulcerative gingivitis
	Tuberculosis	Chronic lesions or ulcerations, usually solitary
	Atypical mycobacterioses	
	Syphilis	Chancre, mucous patches, gumma
	Epithelioid angiomatosis	Macular red/blue mucosal lesions
	Gangrenous stomatitis	Noma, chronic destructive lesions

Dental considerations

Box 2 summarizes the consideration in dental treatment of immunocompromised patients [77,78]. Over the past decade, more individuals with immune deficiencies have been able to function in daily life. Survival of these individuals has increased due to tremendous advances in medical technologies, including improved life-sustaining therapies and medications. Oral health care providers are therefore faced with the challenge of treating a growing number of immunocompromised individuals, many of whom are ambulatory and present to general dentist's offices in our communities. There is an increased need for oral health care providers to treat ambulatory patients who are immune deficient.

It is crucial for the oral health care provider to be aware of potential adverse events that may occur in this group of individuals. Among the most common complications found in immunocompromised patients are infection, bleeding, and side effects from medications or drug therapy. Potential drug interactions should be carefully reviewed before administering medications. Adrenal

Box 2. Dental treatment considerations for immunosuppressed patients

Identify type of immune suppression
- T-cell deficiency: qualitative or quantitative
- B-cell deficiency: qualitative or quantitative
- Phagocytic cells: qualitative or quantitative

Recognize oral complications due to immunosuppressive therapies
- Mucositis
- Salivary gland dysfunction
- Gingival overgrowth
- Radiation-induced trismus
- Treatment-related oral malignancy/neoplasm

Recognize specific opportunistic lesions
- Poor hemostasis
- Poor wound healing
- Drug reactions
- Risk of infection
- Medical stability

Institute treatment modifications
- Antibiotic prophylaxis—type and regimen
- Palliation of musositis
- Stimulation of salivary flow for hyposalivation
- Preventative dental care including fluoride therapy
- Oral hygiene regimen

suppression should also be considered if a patient has been on long-term immune suppression therapy with glucocorticosteroids [79].

The role of the oral health care provider is critical. Oral care is important to the patient's well being and plays a significant part in decreasing the morbidity and complications associated with immune deficiency. It is recommended that the dentist consult and coordinate treatment with the patient's physician to maximize the benefits of oral health care and decrease the potential for treatment-related complications. The oral health care provider should be able to recognize and manage associated oral mucosal disease as well as acute infections. For a review of the diagnosis and treatment of oral complications in immunosuppressed individuals, refer to Epstein and Chow [80]. Systemic or local medications should be administered only in a manner as to avoid opportunistic infection and adverse drug reactions.

Before the initiation of immunosuppressive therapy, a comprehensive oral assessment should be performed that includes a thorough dental and radiographic examination. Oral foci of infection should be identified and eliminated to prevent potential exacerbation and dissemination of infection. Although pre-emptive care is integral in the oral health care of immune-deficient individuals, dental care should be continuous on a routine basis to reduce the complications resulting from the neglect of oral health.

Some patients with an immune deficiency may require antibiotic prophylaxis before and after dental treatment due to the increased risk of local and systemic infection. There is no universally approved protocol for the use of antibiotics for this purpose. The decision to prescribe antibiotics depends on the individual patient's treatment needs, the degree of immunosuppression, the patient's medical stability and prior history of antibiotic therapy. Bacterial cultures and antibiotic sensitivity testing should be considered for chronically immunosuppressed patients and can be valuable information in patients who experience chronic or recurrent infections. Also, bactericidal antibiotics are generally a better choice for this group of patients. Antibiotic therapy should be continued for as long as a patient has open wounds in the oral cavity.

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