



Management of head and neck infections in the immunocompromised patient

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The term *immunocompromised* has traditionally been used to describe patients with a serious impairment of one or more aspects of their immune defense mechanisms. As a result, these patients are more susceptible than immunocompetent hosts to the establishment of bacterial and nonbacterial infections [1]. The number of patients classified as immunocompromised has increased in the last 15 years. Among the many factors contributing to the increased numbers of such patients is the fact that people are outliving once fatal diseases because of advances in modern treatment strategies [2].

The most common conditions leading to an immunocompromised state can be divided into four general categories: systemic conditions, congenital defects or primary immunodeficiencies, iatrogenic causes, and social factors (Box 1). The purpose of this article is to review three common causes of immunosuppression in the oral surgery patient: diabetes mellitus, alcoholism/substance abuse, and HIV/AIDS, with emphasis on their impact on head and neck infections. Each of these conditions leads to a host environment that is more susceptible to severe pathogenic invasion, causing infections such as osteomyelitis, pan-facial abscesses, and necrotizing fasciitis. Management of these infections requires accurate diagnosis, aggressive incision and drainage, proper antimicrobial therapy, and improved nutritional status to achieve resolution.

Normal immune system

To understand the defects in the immune system produced by these conditions, it is first necessary to discuss the immune system in the noncompromised host. The normal functioning immune system involves a complex network of specialized cells and defensive barriers designed to protect an individual from potential pathogens. Its development begins in the first month of gestation with the hematopoietic stem cells located in the yolk sac [3]. In the third month of gestation, hematopoiesis occurs mainly in the liver and continues up to the point when the skeletal elements are formed and the bone marrow becomes the major site of blood cell formation. A variety of cells differentiate from the hematopoietic stem cell, including granulocytes, monocytes, lymphocytes, megakaryocytes, and erythrocytes. Two months into gestation, lymphocytic cells destined to become T cells emigrate from the bone marrow into the developing thymus for maturation. The maturation of B cells occurs under the influence of stromal reticular cells. As the fetus continues to develop, so do the peripheral components of the immune system, including the blood, thymus, lymphatic system, spleen, skin, and mucosa [4].

The immune system is often divided into the innate and adaptive, or acquired immune systems. Innate immunity consists of antigen-nonspecific defense mechanisms activated immediately on encounter with an antigen [5,6]. These mechanisms include physical barriers like epithelium, fatty acids, mucus, and cilia. Soluble factors such as proteins of the complement cascade, chemokines (proteins that

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Box 1. Etiology of immunodeficiency

Systemic conditions

AIDS
 Diabetes mellitus
 End-stage renal disease
 Leukemia/lymphoma
 Systemic lupus erythematosus
 Advanced age

Primary immunodeficiencies

X-linked severe combined immunodeficiency
 Wiskott-Aldrich syndrome
 Chediak-Higashi syndrome
 DiGeorge syndrome

Iatrogenic causes

Immunosuppressive drugs
 Broad-spectrum antibiotics
 Chemotherapy
 Radiation therapy
 Bone marrow transplantation

Social factors

Alcoholism
 Illicit drug use
 Obesity

induce leukocyte migration), cytokines (proteins that modulate leukocyte function), and leukocytes other than T cells and B cells are all part of the innate system that becomes activated in response to the chemical properties of the insulting agent.

Adaptive immunity is a system that is antigen-specific. The main effector cells of this antigen-specific system are the T cells and B cells [7,8]. This system requires antigen processing, which involves the recognition of antigenic epitopes by T cells and B cells, clonal expansion, and differentiation of these antigen-specific lymphocytes into effector cells [9]. In addition, random rearrangement of genes that encode T-cell receptors (TCRs) on T cells and immunoglobulins (Ig) on B cells results in a vast repertoire of antigen-specific receptors. This enables the host to react to thousands of foreign substances [10,11]. Ig genes have the ability to increase specificity and affinity of antibodies by undergoing further somatic mutation. TCR genes do not undergo somatic muta-

tion because their specificity, selected during thymic ontogeny, is retained for self–nonself discrimination. The adaptive immune system can form memory of antigenic exposure, decreasing the time for the subsequent immune response to re-exposure to an antigen. The antigen-driven clonal expansion of T cells and B cells is central to adaptive immunity and is the basis for immunologic memory.

The innate and adaptive immune systems are complementary. For example, the chemokines and cytokines produced by macrophages in an inflammatory reaction serve to attract and modulate T cell and B cell activation and function. In addition, the complement cascade can be activated via the classic pathway by Ig stimulation [12].

The central cellular elements of the immune system are the leukocytes, which consist of granulocytes, specialized antigen-presenting cells, and lymphocytes. Granulocytes include the neutrophils, eosinophils, basophils, and mast cells. The neutrophils, monocytes, and macrophages are responsible for the phagocytic destruction of antigens. Their function is crucial in the acute inflammatory response. Eosinophils play a role in the late phase of allergic inflammation and are responsible for the destruction of parasitic infections. Basophils and mast cells both express IgE and participate in the immediate hypersensitivity immune response. Monocytes, macrophages, Langerhans cells, Kupffer cells, and dendritic cells comprise the antigen processing and presenting cells [13].

There are three major types of lymphocytes: T cells, B cells, and natural killer (NK) cells. T cells are phenotypically defined by the expression of the TCR heterodimeric receptor on their cell surface, which binds antigen displayed by antigen-presenting cells [14]. B cells express transmembrane Ig on their surface, which binds unprocessed antigen independent of antigen-presenting cells. NK cells are morphologically large granular lymphocytes. They are phenotypically defined by the absence of either transmembrane cell surface expression of TCR or Ig and by the presence of the cell surface molecules (protein markers), CD16 and CD56 [15]. T cells and B cells are responsible for clonally specific immune responses, while NK cells provide innate cytotoxic immune responses directed against virus-infected cells and tumor cells. There is also cooperation between the NK cells and the adaptive immune response through Fc-bound IgG and the production of cytokines [4,5].

All nucleated cells of the body display the transmembrane class I human leukocyte antigen (HLA) molecule on their surface, which is encoded by the

major histocompatibility complex. The class I HLA molecule is restricted to presenting linear peptides of 8 to 25 amino acids long to CD8+ T cells [16]. They present endogenous antigens, proteins synthesized within the antigen-presenting cells. These proteins are derived from the processing of genetic information from either viral, intracellular bacterial, or tumor sources. This is consistent with the specificity of CD8+ T cells. Only macrophages, monocytes, dendritic cells, and B lymphocytes present the class II HLA molecule. However, any nucleated cell stimulated with interferon- γ may also express the class II HLA molecule [17]. The specific antigen-presenting cells present only the class II HLA molecule to CD4+ cells. The antigens are exogenous peptides, derived from phagocytized bacteria, parasites and virus particles. Class I and II HLA molecules are cell surface heterodimeric structures with a groove for presentation of linear peptides only. However, there is also a mechanism for the presentation of polysaccharides. CD4 and CD8 T-cells are responsive to lipoglycan antigens presented by CD1 molecules, which are expressed on most antigen presenting cells [18].

The TCR is responsible for the specificity and sensitivity of T cell recognition of antigens presented by the HLA molecule [19]. T cells go through a process of positive and negative selection that occurs in the thymus during T cell development. Positive selection occurs in the cortical region of the thymus. T cells whose antigen receptor fails to bind to self-HLA molecules are programmed to die by apoptosis, whereas T cells whose antigen receptor binds to self-HLA molecules survive and migrate to the medulla. Negative selection occurs next when T cells whose antigen receptor binds to self-HLA molecules with too high an affinity display auto-antigens and undergo apoptosis. This process creates T cells that can recognize HLA molecules correctly but yet not bind to those HLA molecules presenting self antigens [20]. T cells can be further defined by their cytokine production and can be either T helper1 (Th1) cells (which generate cell-mediated immune responses) or Th2 cells (which generate humoral allergic immune responses). Both CD4+ and CD8+ T cells can exhibit either cytokine profile.

The hallmark of the B cell is the production of Ig. Maturation of B cells depends on bone marrow stromal cells and stromal cell-produced interleukin-7 (IL-7) [21]. B cells can express IgM, IgD, IgG1-4, IgE, and IgA1-2 isotypes. IgM and IgD isotypes characterize a naïve mature B cell and switching to the other isotypes is T cell-dependent. B cell membrane Ig and secreted Ig are alternative products of the differentially spliced Ig heavy chain gene. They

are produced when a specific antigen binds to the membrane Ig receptor, which transduces an intracellular signal stimulating clonal expansion to produce more cells and secretes Ig specific for that antigen. This production is a T cell-dependent process, in which these cells direct immunoglobulin isotype switching through a series of cell surface molecular interactions with B cells, resulting in reciprocal intracellular signaling and T cell elaboration of cytokines [22]. Repetitive antigen stimulation is associated with somatic hypermutation within the Ig gene segments, encoding the heavy and light chain variable regions, resulting in Ig with greater antigen specificity. The daughter clones are preferentially expanded and produce antibody with higher affinity, all occurring within the germinal centers of the lymphoid organs.

The complement system facilitates antibody-mediated immunity. The complement system consists of plasma proteins activated along an enzymatic cascade, resulting in a spectrum of bioactive molecules that facilitate opsonization, osmotic lysis of targeted cells, and recruitment of phagocytic cells [23]. Through the classic complement pathway, antigen-antibody complexes efficiently activate the complement cascade. The alternative pathway involves independent activation of cascade protein C3.

Cell adhesion molecules are also very important to the proper functioning of the immune system. Selectins, integrins, and Ig superfamily adhesion molecules are the three families of adhesion molecules that allow leukocytes to attach to extracellular matrices and to adhere to each other. Selectins are found on all leukocytes and function as lectins, which bind to carbohydrate moieties expressed by endothelial cells or other leukocytes. Selectin L, E, and P participate in leukocyte rolling along vascular endothelium. Integrins and Ig superfamily adhesion molecules bind through protein-protein interactions, which is important for stopping leukocyte rolling and mediating leukocyte aggregation and transendothelial migration [31]. The adhesion molecules are often dysfunctional in patients with immunocompromising condition, such as diabetes.

Immune defects in specific diseases

Diabetes mellitus

The negative effects of diabetes mellitus on the immune system have been extensively investigated. These effects impact greatly on the host's ability to prevent the establishment of, and bring resolution to,

a variety of head and neck infections [24,25]. The main etiologic factor in diabetes mellitus that leads to dysfunction in the immune system is hyperglycemia [26,27]. All the major cell types involved in the immune defense are affected. Cellular elements of the innate immune system, including neutrophils and monocytes/macrophages, have altered function. In the neutrophils, functions such as adherence, chemotaxis, and phagocytosis may be down-regulated. This results in a less effective defense against a microbial challenge [28–30]. The neutrophils from diabetic patients also produce less free oxygen radicals, which reduce their ability to make toxic metabolites for release against microbes [8]. Monocytes and macrophages may have up-regulated catabolism of pro-inflammatory cytokines as well as increased production of matrix metalloproteases, such as collagenase [31–33]. This creates an imbalance that is detrimental to the containment of head and neck infections. The hyperglycemic state may also lead to a decrease in fibroblast proliferation and synthesis of collagen, impairing tissue turnover and wound repair [34,35].

It has been proposed that the formation of advanced glycation end-products (AGEPs), which form as a result of glucose irreversibly binding to proteins and lipids in the face of prolonged hyperglycemia, is a key event in the generation of the defects seen in diabetes. [29,33]. Glycation end-products can bind to receptors on various cells, such as leukocytes, and affect their function. The up-regulation of tissue destructive cytokines produced by the monocytes and macrophages may be a result of AGEP binding. AGEPs also alter the solubility of collagen and may play a role in the changes seen in small and large blood vessels. This collagen interaction may result in the accumulation of AGEPs on the basement membrane, affecting the exchange of nutrition, neutrophil migration, and the diffusion of antibodies and oxygen. As a group, these effects should have a detrimental effect on the wound healing apparatus.

There is a significant body of evidence that indicates that cystolic Ca^{++} is elevated in many cell types in patients with both type I and type II diabetes mellitus [36,37]. The high levels of cystolic Ca^{++} , ultimately induced by hyperglycemia, could lead to a reduced ATP content and decreased phagocytic ability in neutrophils [38]. Additionally, increased intracellular Ca^{++} may affect the cellular components of the acquired immune system. B cells may have an impaired proliferative response to mitogen, not unlike that seen in the altered ionic environment of chronic renal failure [39].

Alcoholism

It has been demonstrated that ingestion of large amounts of ethanol leads to a relatively broad impairment of host defense mechanisms [40]. Ethanol impairs phagocytic cells, including neutrophils, monocytes, and macrophages [41]. Also, significant decreases in T cell subpopulations, including CD4, CD8, and CD3, are seen in patients with alcoholic hepatitis [42]. These abnormalities were significantly correlated with protein malnutrition or kwashiorkor-like changes, but not with primary caloric malnutrition or marasmus-like changes. In addition, in this same population, it was noted that a large percentage of patients displayed lowered CD4 cell count numbers (250–300 cells/mm³), which were similar to counts seen in HIV-infected individuals vulnerable to the onset of opportunistic infections. Ethanol seems to blunt the activation of normal human circulating CD3 T cells in terms of their ability to produce IL-2 and thus decreases their proliferative potential in response to mitogenic stimulation. The final stages of CD4 T cell maturation may be impaired, affecting the generation of Th1 and Th2 patterns of cytokine response [43]. It is noteworthy that the most profound impairment in T cell proliferation occurred during the period after cessation of ethanol ingestion when withdrawal symptoms are evident. In this period, there are high levels of corticosteroids in the circulation, suggesting that this may be the primary mode for immunosuppression in alcoholics. An additional subset of T cells, the NK cells, have been shown to be dysfunctional in alcoholic patients, decreasing the hosts ability to eliminate virus-infected cells and tumor cells [44].

B cell activation is dependent on the proper functioning of the T cell and its ability to produce a Th2 cytokine response. If this mechanism is dysfunctional, as has been demonstrated in alcoholic patients, then the production of antigen specific immunoglobulins is greatly reduced [45].

HIV-infected patients

The characteristic immune defect in HIV infection is the destruction of CD4+ T cells [46]. This loss of CD4+ T cells affects a variety of immune cells and their respective functions. CD4+ T cells exhibit decreased lymphokine secretion (IL-2 and interferon- γ) and a decreased response to soluble antigens, increasing susceptibility to opportunistic infections and neoplasms. CD8+ T cells have a decreased cytotoxic response, decreasing a host's ability to fend off intracellular organisms. NK cells have a decreased

ability to kill tumor cells. Macrophages exhibit diminished cytotoxic ability, decreased chemotaxis, reduced IL-1 secretion, poor antigen presentation, and decreased class II HLA antigen expression, contributing to a depressed antigen response and defective wound healing. B cells show depressed Ig production in response to new antigens, and they are refractory to normal signals for B cell activation [47]. There is also polyclonal activation of B cells resulting in hypergammaglobulinemia and circulating immune complexes [48].

A significant number of patients with AIDS will develop neutropenia as a result of direct retroviral infection, use of antiretroviral drugs and other drug therapy, systemic infections, and autoimmune mechanisms [49]. In addition, the neutrophils of patients with AIDS have defective bactericidal function and chemotactic defects [50,51]. Consequently, it has been proposed that the impairment in neutrophil function along with defective immunoglobulin synthesis are important causes of the increased risk of bacterial infections in patients with advanced HIV disease [52]. Also, there has been a strong correlation between the degree of neutropenia and risk of developing serious bacterial infections in cancer patients [53].

Management of infections

The management of head and neck infections in the immunocompromised patient should follow the same basic steps established for immunocompetent individuals. These steps are outlined in Box 2. The

Box 2. Management of head and neck infections in the immunocompromised patient

1. Airway monitoring and possible surgical airway establishment
2. Comprehensive history and physical examination
3. Obtaining appropriate laboratory and imaging studies
4. Empiric antimicrobial therapy
5. Surgical debridement and irrigation, as needed
6. Culture and antibiotic sensitivity testing of infectious organisms to appropriately adjust antibiotic therapy
7. Close follow-up to monitor for resolution and recurrence

first consideration is assuming that there is no acute airway compromise. If the airway is compromised, the first course of action is either oral or nasal endotracheal intubation. In instances where swelling of the oropharyngeal airway is severe, it may be necessary to perform a tracheostomy to establish a competent airway.

Once the airway is secured, the next step should be to obtain a thorough history and physical examination. This provides information about concomitant diseases, social habits, or other processes that may be indications of an immunocompromised status. Such indicators include a positive history of HIV, a previous diagnosis of diabetes, or signs and symptoms of the disease, alcohol or illicit drug use, renal dialysis, and a recent history of recurrent infections. When performing the physical examination, one should keep in mind that immunocompromised individuals may have an attenuated immune response resulting in decreased signs and symptoms of inflammation. Thus, a serious infection may not necessarily have a dramatic clinical presentation.

The next step is to obtain the necessary laboratory and imaging studies to establish the diagnosis and determine the extent of the infection. Routine laboratory studies such as a white blood cell count, hemoglobin and hematocrit determination, a platelet count, and measurement of electrolytes, blood urea nitrogen, creatinine, and glucose should be performed. It is also helpful to obtain a differential white cell count. A high percentage of immature neutrophils would indicate that the immune system is struggling to produce cells to fight the infection. Also, a decreased lymphocyte count may be indicative of an HIV infection. Imaging studies may include plain films, CT scans with or without contrast, MRI, and radionuclide bone scanning (skeletal scintigraphy; see elsewhere in this issue).

Empiric antibiotic treatment should be instituted as soon as possible to rapidly obtain minimum inhibitory concentrations in the plasma. A recommended antibiotic regimen is outlined in Box 3. The initial selection is based on the duration of the infection and the level of immunocompetence of the patient. If the polymicrobial infection has been present for less than 3 days, the amount of cross-colonization or synergy that has developed is limited. After 3 days, enough time has passed so that there is increased virulence of some microorganisms due to the changes in the environment. For example, aerobic bacteria may produce a more favorable environment for anaerobic bacteria, allowing them to multiply more readily. If the infection responds well to the empiric use of an antibiotic, the regimen should be

Box 3. Empiric antibiotic treatment

Early infection (first 3 days of symptoms or mildly immunocompromised)

Penicillin
Clindamycin
Cephalexin (or other first-generation cephalosporin)

Late infection (after 3 days of symptoms or moderately to severely immunocompromised)

Clindamycin (maximum dose)
Penicillin and metronidazole
Ampicillin and sulbactam
Cephalosporin (first or second generation)

Mild, moderate, and severe compromise is based on CD4/viral loads, glycemic control, and the degree of alcoholic-related disease.

Modified from Flynn TR. The swollen face. Severe odontogenic infections. Emerg Med Clin N Am 2000;18: 481–519.

continued even if the culture and antibiotic sensitivity test indicates a change may be appropriate. However, in the absence of clinical improvement, the culture and antibiotic sensitivity test results should form the basis for continued antimicrobial therapy.

If a patient is mildly immunocompromised, there should be an adequate immune response to assist the antimicrobial drug. However, in the moderate to severely immunocompromised patient there is more dependence on the antimicrobial drug to control the infection. Along with the use of antibiotics, surgical debridement or incision and drainage rank as the most important interventions in the management of head and neck infections. This includes removal of all foci of infection (teeth, necrotic tissue, and nonvital bone), exploration and irrigation of all involved fascial spaces, and proper wound care. The lack of vascularity can result in failure of immune effectors and antibiotics to reach the infected sites. Proper placement of drains and periodic irrigation through them is essential for the continuous removal of necrotic debris and enhancement of vascularization. Speci-

mens for culture should be taken at the time of surgical debridement or incision and drainage. Both aerobic and anaerobic cultures should be done and antibiotic sensitivity testing should be performed to provide guidance in selecting the correct antimicrobial treatment. Finally, close postoperative monitoring, including repeated imaging studies, additional surgical interventions, and long-term follow-up are mandatory for resolution of the infection.

Management of head and neck infections involves the contribution of a triad of factors: the host, the antibiotic, and the surgical intervention. In the normal host, serious polymicrobial infections can be produced by organisms that may not be infectious in pure culture but that become infectious through microbial synergism. Consequently, antimicrobial therapy aimed at one major organism may be enough to break the chain and change the environment sufficiently to allow the immune system to take over and bring about resolution of the infection. In the normal host, surgical intervention, as well as antibiotic therapy, significantly alter the microbial environment, allowing the patient's immune system to phagocytize the remaining bacteria. In an immunocompromised patient, the host component of the triad is weakened, leaving the surgeon to rely almost entirely on surgical intervention and antimicrobial therapy to resolve the infection. This is the rationale for recommending aggressive surgical incision and drainage, frequent irrigation of the drains, and use of high-dose, broad-spectrum antimicrobial therapy. Again, it must be emphasized that antimicrobial therapy must be supported by aerobic and anaerobic culturing and antibiotic sensitivity testing.

Summary

The immunocompromised host has a potential increased risk for severe head and neck infections that usually require aggressive antimicrobial therapy and prolonged hospitalization. The causes of the immunocompromised status of patients who seek care from the oral and maxillofacial surgeon are multifactorial and include diabetes, malnutrition, obesity, alcohol abuse, tobacco abuse, intravenous drug abuse, cocaine abuse, HIV infection, and AIDS. Patients with other diseases, such as organ transplant recipients and those receiving cancer therapy or therapy for various autoimmune diseases, are not frequently encountered with severe infections of the head and neck.

The number of patients with multifaceted causes of immunocompromise will clearly increase in the future as the population ages and medical treatments for

previously morbid or lethal conditions are improved. Recognizing the conditions associated with decreased immune function is critical for the proper management of these patients. Concurrent with recognition of immunocompromising diseases, it is important to have a basic understanding of the normal immune system and associated defects, because advances in therapy will undoubtedly increase in complexity. For instance, new antimicrobials, as well as pharmaceuticals that alter cytokine function and affect the generation of progenitor cells in the bone marrow stroma, are on the horizon. Future treatment strategies will not only include aggressive use of traditional management methods but also these new approaches. Ultimately, this should provide a shorter course of treatment and improved outcomes for immunocompromised patients with head and neck infections.

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