Immunology in pediatric dentistry

William C. Donlon, DMD, MA

Abstract

The scope of clinical immunology is ever-increasing. A working knowledge of the immune system and its disease states is important in the evaluation and treatment of pediatric dental patients. This review focuses both on immune conditions with a possible iatrogenic origin, such as allergy, and immune phenomena which the pedodontist may diagnose or treat as part of the medical team.

Due to advances in the science of immunology, patients with defects of the immune system are being diagnosed earlier and living longer. The condition and/or treatment modality may affect the patient’s oral health and delivery of dental care. On a more mundane level, the pedodontist deals with the immune system daily when inquiring about allergies and rheumatic fever in the medical history. Oral immunology affects pediatric dentistry when considering ulcerative lesions of the oral mucosa, juvenile periodontitis, and research areas such as caries vaccination. This paper will present some basic immunological concepts and correlate these with disorders of the immune system pedodontists may confront in practice. Every practitioner should have a working knowledge of immunology and its implications in oral medicine. Many excellent texts can provide practitioners with a review of basic principles and some of these are included in the references. Also, Donlon contains a short review of essential immunology, including the secretory immune system.

Allergy

The evaluation of the child patient for atopic immune reactions is one of the most important, yet potentially difficult, tasks facing the pediatric health care practitioner. A child’s medical history may be vague in references to drug or environmental hypersensitivity. An adolescent may deny any adverse reaction to a previously prescribed medication but develop an allergic reaction. Allergy to one drug may preclude the use of an entire group of substances.

Allergies are divided into two categories: immediate (humoral antibody) or delayed (cellular) responses. These usually are directed against a specific allergen and this substance will always invoke the same type of response although the severity may vary. Another variable is whether the reaction is localized or generalized.

The antibody type which initiates the histamine-releasing immediate atopic reaction is IgE. Molecules of IgE adhere to most cells and basophils causing degranulation and subsequent increase in extracellular levels of vasodilators such as histamine, slow-reacting substance - A, and the kinins. Clinical symptoms are cutaneous wheal and flare, edema, rhinorrhea, tearing, possible respiratory embarrassment, and hypotension (Figure 1).

Antihistamines are the most effective treatment in mild cases. Active therapy of allergy may include induction of IgG antibody synthesis by multiple injections of minute quantities of the allergen. This is done in the hope that circulating IgG will block the secretion of IgE and its sequelae.

Angioneurotic edema is a localized immediate hypersensitivity characterized by swelling of the lips, skin, tongue, and eyes. Airway obstruction is not uncommon. At times, the salivary glands and/or distal extremities also may be involved. The etiology is presumed to be histamine release. Treatment is dictated by the severity of the individual case. A mild reaction will respond to

Figure 1. The diffuse pruritic erythematous lesion seen on this patient’s arm is representative of a total body rash that occurred on the tenth day of a course of sulfa antibiotics for an acute sinus infection. The patient gave a history of allergies to penicillin and erythromycin. The dermatitis medicamentosa was treated with Prednisone and antihistamines.
oral antihistamines while a severe reaction demands maintenance of the airway and acute therapy with intravenous fluid replacement, corticosteroids, and antihistamines.

There is a hereditary form of angioneurotic edema transmitted as an autosomal dominant trait. The defect is in the first step of the complement cascade and an attack may be stimulated by a variety of conditions ranging from emotional upset to trauma. Previously, patients with serious or frequent occurrences of hereditary angioneurotic edema were treated with antifibrinolytic agents such as epsilon-aminocaproic acid, but recently the synthetic androgen, danazol, has been shown to be highly effective. Androgens have the effects of elevating the serum level of C'-1 inhibitor — the basic biochemical defect.

Patients not on chronic drug therapy can undergo dental treatment following preoperative infusion of fresh frozen plasma. If an unsuspected severe episode occurs, the most important emergency steps are airway maintenance, i.e., tracheostomy, and fluid therapy. Intravenous diuretics are helpful in life-threatening attacks. It should be remembered that antihistamines are useless in the hereditary condition and steroids and epinephrine are useful only in a small percentage of cases. A family history is of crucial importance in preventing episodes secondary to dental treatment. Laboratory tests such as the complement decay rate and C'-4 levels are helpful in confirming the diagnosis.

Anaphylaxis is a generalized histamine release secondary to a severe, acute allergic reaction. The patient might have had previous exposure to the antigen and probably will give a positive history of a previous milder allergic response. Most often, the allergy is caused by penicillin or insect stings. The extensive release of histamine affects several organ systems. Its effects on the cardiovascular system is potent vasodilation and increased capillary permeability. This causes hypotension edema, urticaria, and hypovolemia.

In the respiratory and gastrointestinal system, histamine causes smooth muscle contraction. The effects are bronchoconstriction with increased bronchial secretions, and increased GI motility causing nausea and vomiting with increased salivary secretions, respectively. The neurological symptom of pruritis is secondary to cutaneous edema.

Death resulting from untreated anaphylaxis will occur in 3-15 minutes. The initial signs are agitation, sneezing, coughing, itching, and stridor. These will be followed by hypovolemic shock and hypoxia. Convulsions and incontinence precede total cardiovascular and respiratory collapse.

Treatment of an anaphylactic reaction in the dental of-

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*Danocrine, Winthrop Laboratories: 90 Park Ave., New York, N.Y.

*Lasix, Hoechst-Roussel Pharmaceuticals: Somerville, N.J.

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Erythema multiforme is a delayed hypersensitivity reaction which usually involves orofacial signs of contact dermatitis (Figure 2). The allergen is usually a pharmaceutical compound or bacteria. The long period between exposure and clinical manifestations decreases with each exposure and may be as short as a few hours.

Features of contact dermatitis reactions include pruritis at the site, erythema, and bullae. Allergens include estertype local anesthetics, preservatives such as methylparaben, items containing para-aminobenzoic acid (PABA), acrylic monomer, and many other dental materials. Some drugs that frequently are allergenic are penicillin, streptomycin, sulfonamides, barbiturates, aspirin, dilantin, and tetracycline. Oral reactions to drug

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*Benadryl, Parke-Davis (Division of Warner-Lambert Co.): 201 Tabor Rd., Morris Plains, N.J.


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Figure 2. This patient presented with a chief complaint of red, painful swellings and ulcerations of his lips, oral cavity, and extremities. Shown here is a combination of desquamative and erythematous areas of the ventral tongue and mouth floor. The patient gave a history of recently changing jobs and working with new chemicals. This is a typical presentation of erythema multiforme.
compounds, stomatitis medicamentosa, encompass many presenting forms from erythema to purpura and angioneurotic edema.\textsuperscript{12,13}

**Immunization**

Pedodontists treating oral trauma must be aware of the child's vaccination status, most notably tetanus. Infection by the anaerobe Clostridium tetani has a 45-55\% mortality in the United States but is completely preventable by immunization and wound care.

Heat denatured toxin is used for sequential primary immunization. Tetanus toxoid is used as a booster when the patient gives a history of not being vaccinated for at least five years. Boosters produce adequate antibody titers in less than one day. Administering the toxoid to patients more frequently than recommended can produce extremely high antibody levels which can cause urticaria and angioneurotic edema.

In the case of infection, palliative care is rendered, including debridement, antibiotics, antitoxin, and life support (i.e., intubation and sedation). The human globulin tetanus antitoxin neutralizes circulating clostridial neurotoxin but not that which is bound to the motor end-plate.

**Primary Immunodeficiencies**

There is a wide variety of congenital immune-system abnormalities with which the pediatric dentist must be familiar. Due to ever-improving modes of therapy, some of these patients are living longer and require dental care. For a child with a deficient immune mechanism, every infection is potentially fatal. Therefore, each requires the most careful diagnostic and clinical care.

Major presentations of immunodeficiencies are: (1) increased frequency of infections, (2) unusually severe infection, (3) prolonged duration of infection, (4) unexpected complication or manifestation, and (5) infection with a minor pathogen\textsuperscript{14} (Figure 3). For example, a child with an acute pulpitis or dentoalveolar abscess rapidly could develop an acute osteomyelitis. In chronic mucocutaneous candidiasis, (La Tilell deficiency) the oral thrush is unresponsive to treatment almost totally. In chronic mucocutaneous candidiasis, (La Tilell deficiency) the oral thrush is unresponsive to treatment almost totally. In chronic mucocutaneous candidiasis, (La Tilell deficiency) the oral thrush is unresponsive to treatment almost totally.

Primary immunodeficiencies are subdivided into humoral and cellular types. Patients with DiGeorge's syndrome, Swiss-type agammaglobulinemia, and Wiskott-Aldrich syndrome will have diminished or absent antibody synthesis. Those with thymic aplasia, ataxia telangiectasia, or chronic mucocutaneous candidiasis will have inadequate delayed immune reactions.

Screening tests include complete blood count (noting leukocyte morphology), immunoglobulin levels, Schick test, isoagglutinin (anti-A, anti-B) titers, spleen scan, cultures, sedimentation rate, and radiography.\textsuperscript{15} The chest film is examined for thymic shadow, narrowing of anterior mediastinum, and/or right-sided aortic arch as seen in thymic hypoplasia.

Pedodontists and orthodontists should note that cephalometric radiographs can be useful. Patients with antibody deficiencies will have decreased adenoidal tissue on lateral skull and facial views (Figure 4).

Micronathia is characteristic of DiGeorge's syndrome. Other signs include thymic hypoplasia, hypertelorism antimongolid slant of the eyes, ear malformation, and hypoparathyroidism. In Swiss-type agammaglobulinemia, fungal superinfection of the mucous membranes and skin is the first sign. The clinical picture may mimic Letterer-Siwe disease.

In chronic mucocutaneous candidiasis, candida overgrowth is usually present in the oral cavity. Only rarely does the infection become systemic. Local antifungal agents are the least effective therapy. Successful modalities include intravenous amphotericin, lymphocytic infusions, and transfer factor.\textsuperscript{16} A variety of diseases (Hodgkin's, measles, multiple myeloma) and treatment modalities (irradiation, antibiotics, antimitabolites) may cause secondary immune deficiencies. In Hodgkin's disease, there is a high incidence of localized and disseminated candidiasis. Eight per cent of patients have herpes zoster episodes, usually as a localized erup-

![Figure 3](image-url) This is a case of secondary immunosuppression and resultant infection. The infant had a rhabdomyosarcoma, which was being treated with chemotherapy. A staphylococcal infection ensued which progressed rapidly and required aggressive medical and surgical management.

![Figure 4](image-url) Lateral skull and cephalometric radiographs may provide a clue in the investigation of immunodeficiencies. Patients with agammaglobulinemias will have hypoplastic B cell lymphoidal tissue. This includes the adenoids, which are seen in the anterior nasopharynx and can be localized inferoposterior to the pterygomaxillary fissure. Shown here is an immunological competent 16-year-old female.
tion. Anticonvulsants, such as phenytoin, can cause atypical lymphoid hyperplasia.¹⁵

Autoimmunity

A wide variety of clinical entities currently are thought to have an autoimmune pathogenesis. Most are grouped under the general heading of "collagen diseases." The anti-self antibodies are produced by "forbidden" clones of lymphocytes which overcome homeostatic immune-system regulation. Cellular phenomena are also a part of autoimmune diseases.

Most autoimmune states occur predominantly in adults but those that manifest in children can be severely debilitating and potentially fatal. The patient first may present to a dental office since oral complications may be an early sign.

Lupus erythematosus may present in adolescents in the systemic or discoid form. Both forms frequently have orofacial involvement (Figure 5). Skin lesions usually precede those of the mucous membrane.

Figure 5. This combined red and white lesion of the buccal and oropharyngeal mucosa is lupus erythematosus of the discoid variant. The manifestations of the disease in this patient were almost exclusively orofacial.

Pathognomonically, the bullae of lupus increase in size by peripheral growth. Generally, treatment consists of systemic anti-inflammatory agents.

Pemphigus vulgaris is a bullous mucocutaneous disease with an autoimmune etiology. Immunofluorescent studies demonstrate antibodies to stratified epithelium. The condition is extremely rare in children, but in almost all reported cases the oral cavity is the site of origin. Bennett and coworkers²⁷ recently reviewed the literature and presented a new case occurring in an eight-year-old.

Several authors have suggested that common oral lesions are secondary to autoimmune antibody production, i.e., aphthous stomatitis and Behcet's syndrome.

Myasthenia gravis is an autoimmune condition characterized by muscle degeneration. Presenting facts include multiple autoantibodies, thymic hyperplasia, and other concomitant autoimmunity. The juvenile form comprises 1% of all cases. The initial symptom is usually ptosis, followed by facial weakness and mild respiratory embarrassment.

Rheumatoid arthritis may occur in childhood with the typical joint lesions. Temporomandibular joint symptoms may or may not be present. Several autoimmune blood dyscrasias may occur in childhood or adolescence: pernicious anemia, autoimmune hemolytic anemia, and idiopathic thrombocytopenic purpura are among them. Oral manifestation of these diseases is gingival hemorrhage with or without other mucosal lesions. Petechiae and ecchymosis may occur on the palate.

Connective tissue disorders of the salivary glands may occur in children. Prepubertal Sjögren's syndrome has been reported.¹⁹ The keratoconjunctival sicca may develop in a child with other autoimmune disease.¹⁹ Treatment is usually palliative. Regular oral physiotherapy is necessary to prevent rampant caries in patients with xerostomia.

Periodontosis

The etiology of juvenile periodontitis has been debated and remains highly speculative. Recent reviews by Rubin,²⁰ and Vogel and Deasy,²¹ thoroughly present the broad scope of current knowledge and opinion regarding this disease. The work of Lehner and coworkers²² has provided a cornerstone for the implication of immune dysfunction in the pathogenesis of periodontitis. Antigens of normal oral microflora do not stimulate in vitro mitosis and differentiation of T cells from patients with juvenile periodontitis. Alteration of immunoglobulin levels also has been noted. Cianciola and coworkers²³ reported a depression of neutrophil phagocytosis and chemotaxis in this disease.

Some workers²¹,²⁴ have suggested limiting the designation of periodontitis to acute periodontal disease in pediatric patients who are otherwise healthy. This author finds such a classification to be an antithesis of the modern concept of autoimmune disease. Patients with one of these diseases are more prone to other such conditions. Rubin²⁰ and Cianciola²³ outline a variety of immune system disorders which are predisposing factors in periodontal disease. The child with other syndromes should make the diagnostician weigh periodontosis more heavily in the differential diagnosis. For more than 50 years, one variety of periodontosis has been linked with hyperkeratosis palmaris et plantaris in Papillon-Lefèvre syndrome.²⁵ This syndrome may be associated with or similar to other connective tissue diseases.

Rheumatic Heart Disease

Great emphasis has been placed on the prevention of subacute bacterial endocarditis (SBE) in dental education. One sequela of SBE is autoimmune valvular damage. Macroscopic accumulations of streptococci on the damaged valves are called vegetations. This autoimmune
Pedodontists are an important source of patient referrals for orthodontists since 78% are of the Diplomates refer patients to orthodontists or have an orthodontist associated with their practice.

The character of pedodontic practice is changing. Most pedodontists report their patients require fewer traditional pedodontic procedures than they did five years ago. Only about one-third of the pedodontists report that their practices have grown in the past five years. These findings are in agreement with those reported in the North Carolina survey.1 The findings likely result from the interaction of the increased number of dental graduates, and the decline in the economy, birth rate, and caries incidence. The changing needs for traditional pedodontic services undoubtedly has encouraged some pedodontists to look outside the traditional scope of pedodontic procedures to expand their practice. These trends have important implications for pedodontic advanced education programs, continuing education for practicing pedodontists, and the future role of the specialty of pedodontics.

All correspondence regarding this manuscript, including requests for reprints should be sent to Dr. Arthur J. Nowak, Department of Pedodontics, University of Iowa Dental School, Iowa City, Iowa 52240.