Adverse Drug Reactions - Part II

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Conflict of Interest Disclosure Statement

- The author report no conflicts of interest associated with this course.

Introduction

Adverse drug reactions (ADRs) may be characterized as (1) "on-target," (2) "off-target," (3) cytotoxic reactions, (4) immune-mediated reactions, and (5) idiosyncratic reactions.1 This course discusses common immune-mediated and idiosyncratic ADRs related to the top 200 drugs dispensed by U.S. community pharmacies in 2008 to inform and raise the awareness of oral healthcare providers of the spectrum of potential ADRs affecting their patient cohort. A discussion of less common ADRs that relate to dental therapeutics and/or manifest in the head and neck area is also provided.

Please note that this is Part II of a two-part series. *Adverse Drug Reactions – Part I* discusses common "on-target," "off-target," and cytotoxic reactions related to the top 200 drugs dispensed by U.S. community pharmacies in 2008, and less common ADRs that relate to dental therapeutics and/or manifest in the head and neck area.

Course Contents

Overview

The global objectives of the course are to present the mechanisms of adverse drug reactions (ADRs) characterized by immune-mediated reactions and idiosyncratic reactions; provide a clinical frame of reference for ADRs; and raise the level of awareness of oral healthcare providers of the spectrum of potential ADRs affecting oral tissues and various organ systems.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Discuss, in general terms, the mechanisms of immune-mediated, idiosyncratic, oncogenic, teratogenic, and secondary ADRs.
- Discuss the spectrum of potential immune-mediated, idiosyncratic, oncogenic, teratogenic, and secondary ADRs.
- Discuss issues related to preventing, diagnosing, and reporting ADRs.

Introduction

Drugs seldom exert their beneficial effects without also causing one or more **adverse drug reactions** (ADRs). Major mechanisms of ADRs include (1) "on-target" adverse reactions, (2) "off-target" adverse reactions, (3) cytotoxic reactions, (4) immune-mediated reactions, and (5) idiosyncratic reactions.[1] In Adverse Drug Reactions – Part I, the discussion focused on mechanisms (1), (2), and (3) and related common ADRs that can occur with therapeutic doses of drugs in the top 200 dispensed by U.S. community pharmacies in 2008.[2]

In Adverse Drug Reactions – Part II, the discussion is extended to discuss (4) immune-mediated reactions, (5) idiosyncratic reactions, and related common ADRs that occur with drugs in the top 200 dispensed by U.S. community pharmacies in 2008, and less commonly noted ADRs affecting oral tissues. In addition, a brief discussion of the mechanisms of uncommon, time-related (delayed), and usually dose-related ADRs, i.e., carcinogenesis and teratogenesis, and some secondary ADRs is presented.

Immune-mediated Mechanisms of ADRs

There are three major categories of ADRs related to the immune system: immunotoxicity, autoimmune reactions, and hypersensitivity or allergic reactions.[1] **Immunotoxicity** may be the specific intent of therapy, e.g., when monoclonal antibodies target specific B cells. Alternatively, it may occur as an ADR to therapy when cytotoxic agents designed to kill malignant cells also damage normal cells in the bone marrow and lymphoid tissues. Immunotoxicity may generate secondary ADRs, e.g., infections and oncogenesis.

Drugs can also initiate **autoimmune reactions** resulting in a person's immune system attacking his/her own cells. For example, a drug may elicit an antibody response to Rh factors on red blood cells (RBCs), causing hemolytic anemia; or induce an antibody response to myeloperoxidase or DNA, causing a lupus-like syndrome; or directly cause mast cell degranulation, resulting in urticarial lesions; or cause blistering lesions of the skin and mucous membranes, e.g., erythema multiforme or Stevens-Johnson syndrome.

Hypersensitivity or **allergic reactions** reflect drug-related immunogenicity. Therapeutic

peptides or proteins with molecular weights >600 daltons are recognized by the immune system as foreign substances and can directly trigger allergic reactions. Drugs with molecular weights <600 daltons are too small to act as direct immunogens; however, these drugs may act as **haptens**. Haptens bind covalently to large endogenous proteins and the hapten-protein complex triggers the allergic response.

The Gell-Coombs classification system proposes four mechanisms of hypersensitivity or allergic reactions: type I or immediate hypersensitivity reactions (anaphylaxis), type II or antibody-dependent cytotoxic reactions, type III or immune complex-mediated reactions (serum sickness), and type IV or delayed T cell-mediated reactions.[1,3] An allergic response is predicated on sensitization, i.e., prior exposure to a drug. At highest risk are adults, women, patients with HIV infection, and those with a history of allergy to related drugs.

Type I or **immediate hypersensitivity reactions** (anaphylaxis) are predicated on exposure to an allergen and antigen-specific antibody production dominated by immunoglobulin E (IgE) isotype.[1,3] Upon re-exposure IgE antibodies bind to mast cells in mucosal and epithelial tissues (Figure 1). The simultaneous binding of an antigen to adjacent IgE molecules fixed to Fc receptors triggers degranulation of mast cells, resulting in the production and release of histamine, leukotrienes, prostaglandins, and cytokines.

Type II or **antibody-dependent cytotoxic reactions** are predicated on exposure to an allergen and antigen-specific antibody production dominated by immunoglobulin G (IgG) or M (IgM) isotypes.[1,3] Upon re-exposure the antigen binds to the surface of target cells (usually RBCs), the antigen-antibody complexes attract cytotoxic T cells, which release chemical mediators that cause target-cell lysis (Figure 2). Alternatively, antigen-antibody complexes attached to target-cells may activate complement-mediated target-cell lysis.

Type III or **immune complex-mediated reactions** (serum sickness) are predicated on exposure to an allergen and antigen-specific antibody production dominated by immunoglobulin G (IgG) or M (IgM) isotypes.[1,3] Upon re-exposure, soluble drug molecules form large insoluble antigen-antibody complexes that are deposited in target tissues (e.g., kidneys, joints and lungs) and initiate complement activation, neutrophil and platelet aggregation, and an intense inflammatory response (Figure 3).

Type IV or **delayed T cell-mediated hypersensitivity reactions** are predicated on exposure to haptens, which bind to

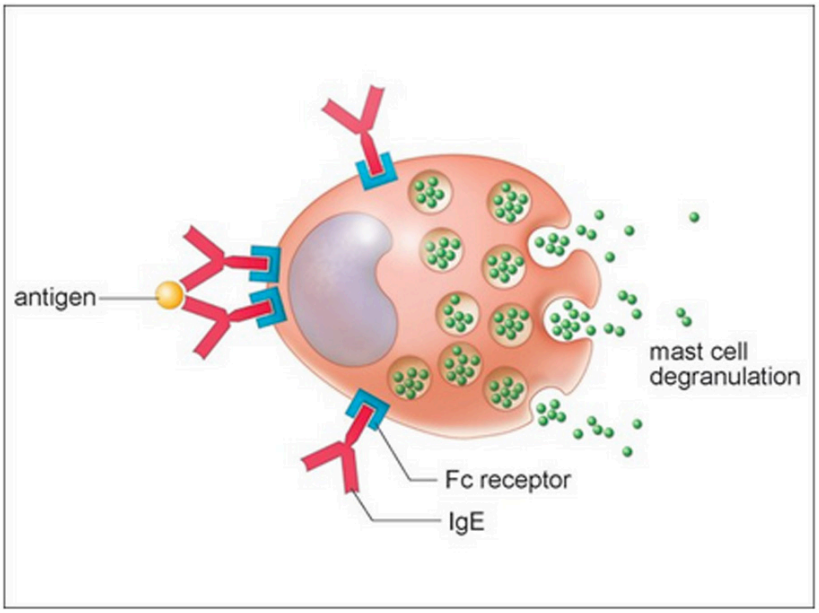


Figure 1. Type I or Immediate Hypersensitivity Reaction.

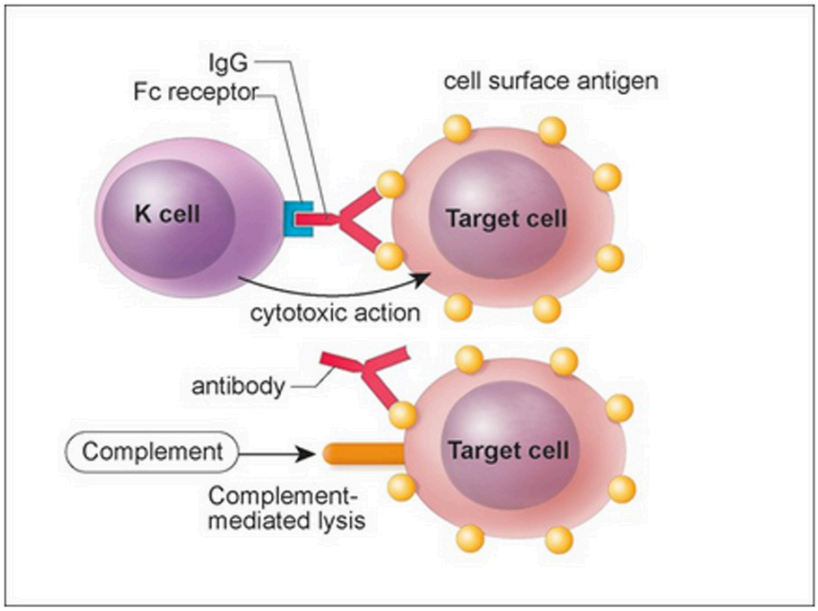


Figure 2. Type II or Antibody-dependent Hypersensitivity Reaction.

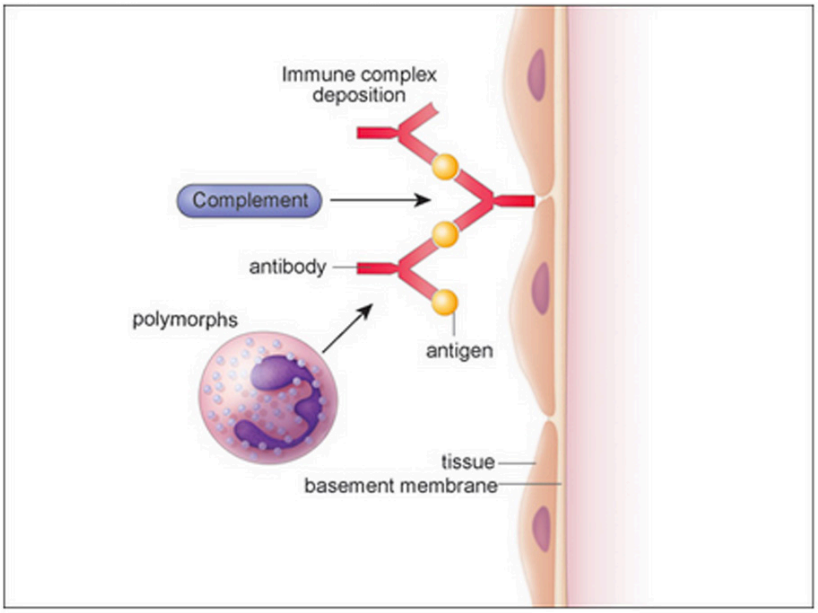


Figure 3. Type III or Immune Complex-mediated Reaction.

endogenous macromolecules and form hapten-protein complexes.[1,3] Langerhans cells phagocytize and process hapten-protein complexes, load them into major histocompatibility complexes, migrate to regional lymph nodes, and present them to naïve T-lymphocytes. Upon re-exposure sensitized T cells in target tissues activate macrophages, which mediate direct cellular damage (Figure 4).

Mechanisms of Idiosyncratic ADRs

Idiosyncratic ADRs are unpredictable and affect a small number of patients. Factors influencing drug response phenotype include age, gender, underlying disease, and genetic and epigenetic mechanisms.[1,4,5] Genetic polymorphism and epigenetic factors (i.e., heritable changes in gene function and expression not related to DNA sequencing) influence the outcome of

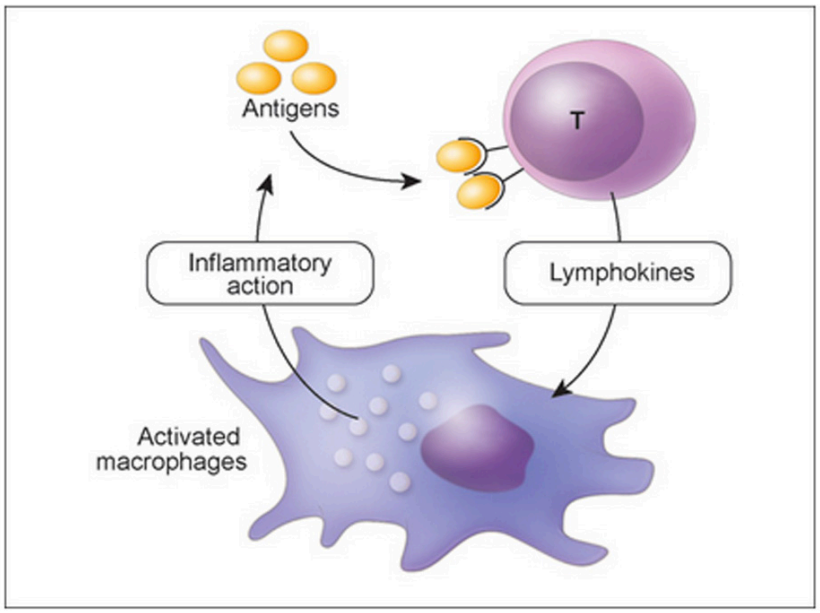


Figure 4. Delayed T Cell-mediated Hypersensitivity Reaction.

pharmacotherapy and have been implicated in pharmacokinetic and pharmacodynamic variations.

Inherited variations in enzymes that catalyze drug metabolism are the most common causes of variation in response to medications. The effects of genetic polymorphism on drug metabolism are the most prominent with five isoforms of the cytochrome P450 enzymes, i.e., CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Isoenzyme-induced variations in drug metabolism may lead to significant differences in the efficacy and toxicity of drugs.

Mechanisms of Oncogenic ADRs

Oncogenesis is a complex process involving genetic and epigenetic changes that result in an imbalance between cell division and apoptosis (programmed cell death).[1] Among the known factors implicated as potential "initiators" and/or "promoters" of cancer are tobacco, alcohol, solar radiation, ionizing radiation, occupational carcinogens, environmental pollutants, infectious agents, nutrients, and rarely, medications.

Primary oncogenic effects can be produced by drugs (initiators) that damage DNA or by drugs (promoters) that facilitate the proliferation of cells carrying precancerous mutations.[1] Drugs that act as initiators are drugs that have been converted into reactive metabolites by polymorphic oxidation reactions. These reactive metabolites bind covalently to DNA in proto-oncogenes or tumor-suppressor genes, modify DNA, and lead to mutations.

Proto-oncogenes are normal genes that promote cell division. **Oncogenes** are proto-oncogenes, that through amplification or mutation, become permanently activated allowing abnormal cells to survive and proliferate. **Tumor suppressor genes** are normal genes that slow down cell division, repair damaged DNA, or initiate apoptosis. Through mutations, tumor suppressor genes are inactivated leading to uncontrolled cell growth.

For example, activated oncogenes and inactivated tumor suppressor genes may alter the expression of cell-cycle regulatory proteins (e.g., cyclin-dependent kinases) that govern the initiation, progression, and completion of cell-cycle events, causing overexpression of cyclins and loss of expression of cyclin-dependent kinase inhibitors. Deregulated cyclin-dependent kinase activity provides malignant cells with a selective growth advantage.

Secondary oncogenic effects are related to therapeutic immunosuppression. Reactivated **latent oncogenic viruses** can induce mutations, gene amplifications, or chromosome

rearrangements in host DNA.[6] There are seven known human oncogenic viruses (Table 1). Human oncogenic DNA viruses include the Epstein-Barr virus, human papilloma viruses, hepatitis B virus, and herpes simplex virus-8, and Merkel cell polyomavirus. Human oncogenic RNA viruses include human T-lymphotropic virus type 1 and hepatitis C virus.

Mechanisms of Teratogenic ADRs

Teratogenesis is the process that results in structural and/or functional defects in a fetus.[1,7] A **teratogen** is any agent that can induce teratogenesis. While drugs are most frequently implicated, other potential teratogens include: radiation exposure, Zika virus, and lead exposure. Overall, an estimated 5% of birth defects are believed to be caused by a known teratogen.[7] Drug teratogenicity depends on the ability of the teratogen to diffuse from the maternal circulation across the placenta. The extent of diffusion depends on the chemical nature of the agent (molecular weight, protein binding capacity, lipid solubility, and pKa) and maternal pharmacokinetic factors.

Teratogens present the greatest risk to the embryo during periods of intense mitotic activity. Exposure to a teratogen from the time of conception to day seventeen results in spontaneous abortion. Exposure to a teratogen during organogenesis, i.e., from day 18 to day 55 results in developmental abnormalities (Figure 5). The period from day 55 through the 3rd trimester is a period of fetal growth, during which exposure to a teratogen affects organ function.

Clinical Manifestations of ADRs

Table 1. Human Oncogenic Viruses[6]

Virus Type	Virus	Associated Malignancies
DNA	Epstein-Barr virus	Hodgkin lymphoma (40%) Burkitt lymphoma (95%) Gastric carcinoma (10%) Nasopharyngeal carcinoma (most) Other lymphomas
	Human papillomavirus	Cervical carcinoma (>95%) Oropharyngeal carcinoma (70%) Anogenital carcinomas
	Hepatitis B virus	Hepatocellular carcinoma (>50%)
	Herpes simplex virus-8	Kaposi (99%)
	Merkel cell polyomavirus	Merkle cell carcinoma (80%)
RNA	Human T-lymphotropic virus 1	Adult T cell lymphoma (99%)
	Hepatitis C virus	Hepatocellular carcinoma (25%) Non-Hodgkin B cell lymphomas

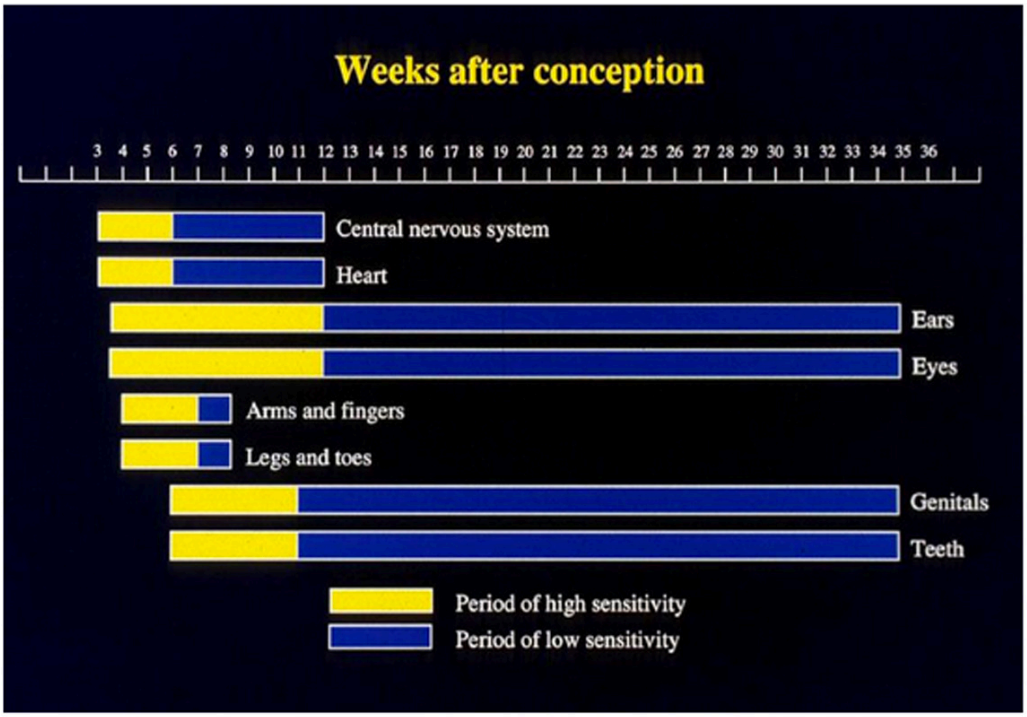


Figure 5. Periods of Increased Organ-specific Sensitivity of Fetal Tissues to Teratogens.

The Council of International Organizations of Medical Sciences (CIOMS) published guidelines on diagnostic criteria and basic requirements for standardized reporting of ADRs.[8] This is especially relevant since most reporting is based on single cases. The CIOMS codified ADRs under 21 major headings and defined 179 reportable conditions. However, there is no specific major heading for ADRs affecting oral tissues.

ARDs related to immune-mediated and idiosyncratic mechanisms among the 30 most common ADRs associated with therapeutic doses of drugs in the top 200 dispensed by U.S. community pharmacies in 2008 include rash, pruritus, allergic reactions, urticaria, arthralgia, and anaphylaxis.[9] In addition, less common ADRs affecting oral tissues, rare oncogenic and teratogenic ADRs, and some secondary ADRs are presented.

DailyMed is the official website for FDA-approved label (package insert) information.[10] It provides a centralized, standard, comprehensive, up-to-date, look-up-and-download resource for package inserts submitted to the FDA by pharmaceutical companies. The website is user-friendly, includes strengthened warnings undergoing FDA review, and is a reliable resource for information on known potential ADRs related to specific drugs.

ADRs Affecting Skin (Mucosa) and Appendages

Rash was the 6th most common ADR associated with the top 200 drugs dispensed by U.S. community pharmacies in 2008.[9] However, rash is a general term and CIOMS discourages its use as it encompasses virtually all skin eruptions.[8] **Pruritus** or itching was the 10th most frequently cited ADR and may be a symptom of primary skin lesions or less frequently that of a systemic disease.[11] However, itching may also be the result of drug-induced histamine release by mast cells unrelated to the immune system or it may reflect a bona fide drug-related allergic reaction.[11]

Opioid analgesics, especially when used for epidural and intrathecal anesthesia, frequently induce pruritus and also have the ability to induce peripheral histamine release.[12] Vancomycin and ciprofloxacin can cause **red man syndrome** which is characterized by itching followed by the emergence of a "rash" or hives, i.e., urticaria.[1] Other drugs that can cause itching and urticaria include NSAIDs, penicillin, and some antifungal agents. These reactions are unrelated

to IgE-induced mast cell degranulation and have been called **anaphylactoid** or **pseudoallergic reactions**.[8]

Urticaria the 16th most frequently reported ADR reported in 2008, is a well-circumscribed erythematous, pruritic plaque on skin associated with the release of histamine and other vasoactive substances from mast cells and basophils, resulting in intradermal edema caused by vasodilation.[8,9,12] As noted, this may be due to direct non-allergenic activation of mast cells by drugs or drug-induced cyclooxygenase inhibition-related mast cell degranulation. **Chronic urticaria** (> 6 weeks) is usually idiopathic or may be associated with auto-antibodies to IgE receptors causing mast cell degranulation.[12]

Acute urticaria (< 6 weeks) most often reflects a hypersensitivity or allergic reaction in which allergen-bound IgE initiates mast cell and basophil degranulation (Figures 6 and 7).[12] It may be noted in susceptible patients within minutes or hours following exposure, usually by contact or inhalation to an allergen such as latex proteins, and it may be precipitated by exposure to many prescription and over-the-counter medications. A common feature of pruritus and urticaria is subcutaneous and submucosal angioedema of target tissues.[8,12]

Angioedema is a swelling (usually localized) of the subcutaneous tissues usually mediated by either mast cell–derived mediators (e.g., histamine, leukotrienes, prostaglandins) or bradykinin and complement-derived mediators.[13] A few cases are hereditary. Angioedema may be acute and chronic. **Acute angioedema** (< 6 weeks) is mast-cell mediated in >90% of cases. While it may be localized, swelling of the extremities, face, lips (Figure 8), tongue, oropharynx (Figure 9), and larynx along with stridor, wheezing, and hypotension are harbingers of anaphylaxis.[8,13] Another important variant of acute angioedema is caused by increased bradykinin activity associated with angiotensin-converting enzyme (ACE) inhibitors. The face and upper airways are most affected, but urticaria does not occur. This variant is estimated to account for up to 30% of cases of acute angioedema presenting to emergency

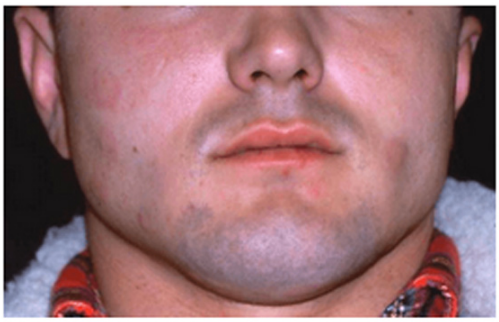


Figure 6.

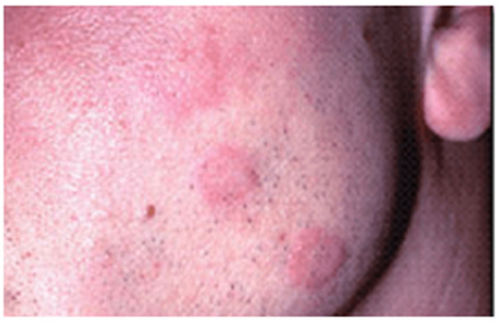


Figure 7.

Acute urticaria following the oral administration of penicillin.

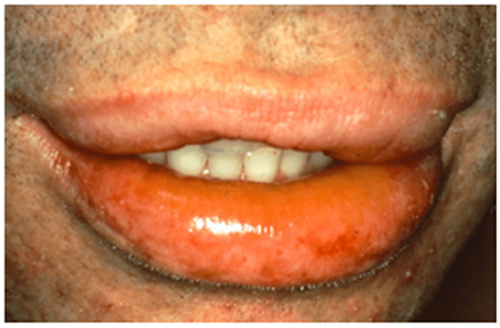


Figure 8.

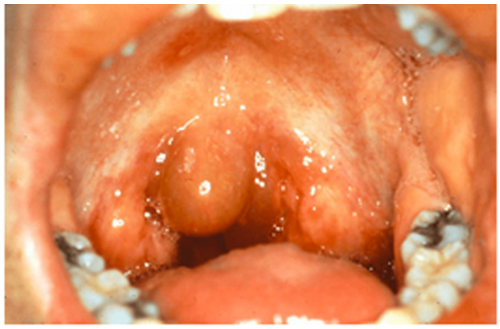


Figure 9.

Acute angioedema of the lips and oropharynx following the oral administration of penicillin.

departments and may occur soon or years after ACE inhibitor therapy initiation. **Chronic angioedema** (> 6 weeks) is rarely IgE-mediated; it is usually idiopathic and may be caused by the chronic ingestion of certain drugs (e.g., penicillin), preservatives, milk, and food additives; and a few cases are hereditary.[13]

A specific mucocutaneous ADR of interest to oral healthcare providers is **erythema multiforme** (EM).[14-16] EM is an acute T cell-mediated cytolytic reaction to immune-complex mechanisms involving antigen-antibody reactions that target small blood vessels in the skin or mucosa. About 90% of cases are precipitated by infection, with the herpes simplex virus most frequently implicated. Other precipitating or triggering factors include medications (e.g., sulfonamides, NSAIDs, penicillins, anticonvulsants), foods, food additives, and inflammatory bowel disease. Cutaneous lesions begin as erythematous papules that progress to form the more characteristic iris or target lesions (Figure 10).[14-16] Hemorrhagic crusting of the lips (Figure 11) and vesiculoerosive lesions on unattached oral mucosal tissues are considered pathognomonic.

The previously associated potentially fatal **Stevens-Johnson syndrome** (SJS) and **toxic epidermal necrolysis** (TEN) are now considered separate entities from EM.[16,17] The majority of SJS and TEN cases are precipitated by drugs or toxins. Oral features of SJS and TEN are similar to those associated with EM. The major difference between SJS and TEN is the distribution of dermal lesions. SJS affects <10% of the body surface while TEN affects >30%. Skin involvement of 10% to 30% of the body surface is considered SJS-TEN overlap.[14]

Extrinsic antigenic sources such as drugs have been identified as agents responsible for oral lichen planus (OLP)-like lesions. Drugs such as NSAIDs and ACE inhibitors can act as haptens and alter the antigenicity of epithelial self-antigens. Suspected OLP that can be traced to an extrinsic cause is not OLP, but a **lichenoid reaction**.[8,16] Oral lichenoid lesions most often affect the buccal mucosa (Figures 12 and 13), gingivae, and the lateral border of the tongue and may be "reticular", atrophic, or erosive. **Arthralgia** was the 24th most commonly reported

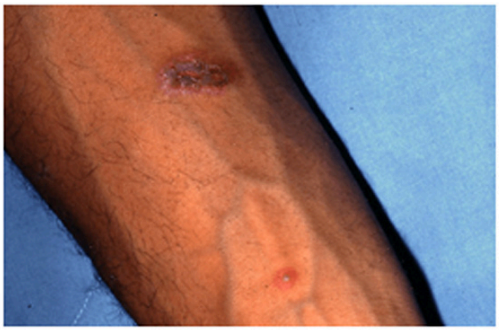


Figure 10.

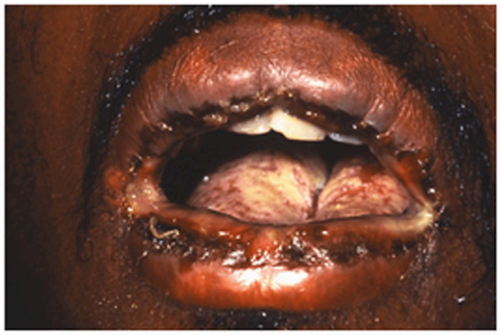


Figure 11.

Characteristic iris or target skin lesions and serohemorrhagic crusting of the lips associated with erythema multiforme following the administration of ibuprofen.

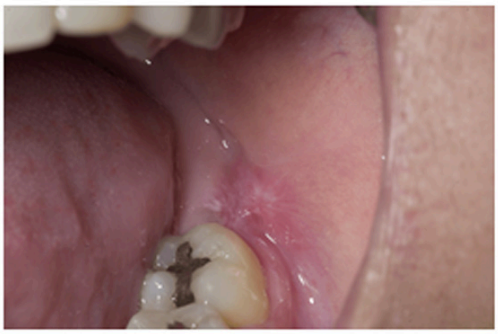


Figure 12.

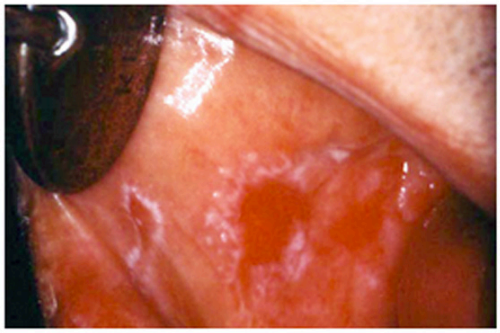


Figure 13.

Lichenoid lesions in a patient with rheumatoid arthritis taking ibuprofen.

ADR associated with the top 200 drugs in 2008.[9] Arthralgia may be described as sharp or dull, stabbing, burning or throbbing, and may range in intensity from mild to severe. A large and heterogeneous group of drugs have been implicated, including antimicrobials, anti-mycobacterials, antifungals, antidiabetics, chemotherapeutics, retinoids, cytokines, and psychotropics. Not surprisingly, no predominant pathogenetic mechanism has been identified.[18] The most common cause of arthralgia is arthritis; other causes include injury and infection.

Hypersensitivity-related ADRs

Type I hypersensitivity reactions or anaphylaxis are acute, IgE-mediated systemic reactions that occur within minutes to hours after parenteral or enteral administration of a drug in a previously sensitized patient.[1,3,16] The shorter the reaction time, the more severe the reaction is. Following enteral administration of an allergen the reaction may be delayed or less severe. Anaphylaxis may simultaneously involve multiple organ systems, manifesting one or more of the following signs and symptoms:[8,16]

- Skin: pruritus, erythema, urticaria, angioedema
- Respiratory system: laryngeal edema and/or spasm, bronchospasm
- Gastrointestinal system: abdominal cramps, vomiting, diarrhea
- Central nervous system: anxiety, agitation, loss of consciousness
- Cardiovascular system: tachycardia or bradycardia, hypotension, shock

Type II antibody-dependent hypersensitivity or **cytotoxic reactions** occur when a drug binds to target cells, usually RBCs, and is recognized by IgG or IgM antibodies.[1,3,16] The time required for cytotoxic T cell-mediated target cell lysis or target cell lysis mediated by the complement system in response to a specific antigen is variable. Clinical manifestations include hemolytic anemia, neutropenia, and thrombocytopenia. Type II reactions are rare, but may be precipitated by several drugs such as penicillin.

Type III or **immune complex–mediated hypersensitivity reactions** (serum sickness) may occur within 7-10 days after initial exposure to a heterologous (nonhuman) protein such as Rabies vaccination, immune modulating agents (i.e., rituximab, infliximab) and anti-venoms.1,3,19 Any subsequent re-exposure results in a quicker onset of serum sickness. Serum sickness-like reactions do not involve immune complex formation, and the most commonly implicated agents are penicillins, cephalosporins (most commonly cefaclor), tetracycline, sulfonamides, bupropion, fluoxetine, and thiouracil. (Figure 14 and 15).

Common signs and symptoms of serum sickness include fever, cutaneous eruptions (usually urticaria), arthralgia, headaches, myalgia, dyspnea and wheezing, and lymphadenopathy.[19] Angioedema of the face and neck may occur. Serum sickness is typically self-limiting and resolves within 1-2 weeks after removal of the offending agent.[15,19]

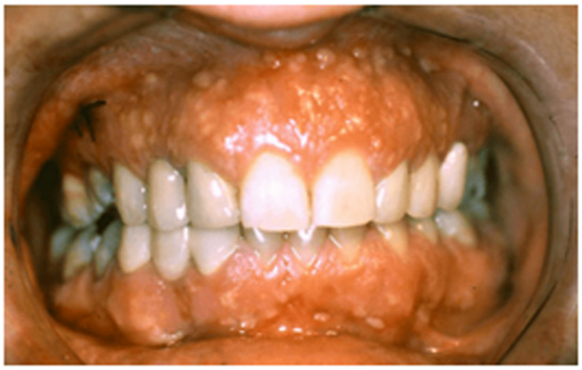


Figure 14.

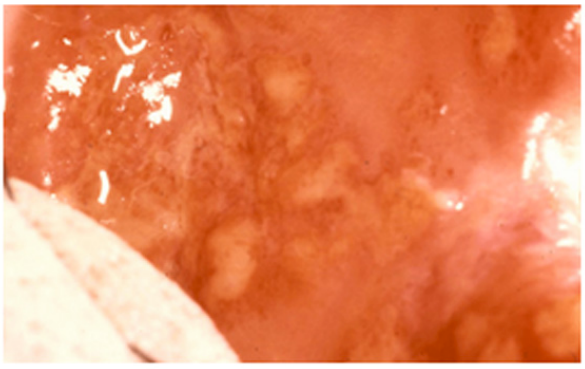


Figure 15.

Type III or immune complex-mediated hypersensitivity reaction with vasculitis in response to tetracycline therapy.

Type IV hypersensitivity or delayed T cell-mediated reactions are mediated by immunologically committed T lymphocytes. In susceptible patients, cytokines and other mediators of inflammation are released within 2 to 7 days of re-exposure to an allergen.[1,3,20] Clinical manifestations include allergic contact dermatitis/mucositis (Figures 16 and 17) or a drug-induced maculopapular rash. With repeated antigenic challenge, the response becomes more profound, including fever, malaise, and angioedema in target tissues.

Idiosyncratic ADRs

As noted earlier, idiosyncrasy is an unpredictable reaction of any intensity observed in a small number of the individuals.[1,4] When a drug produces its usual effect on a person at an unexpectedly high dose, the patient is said to be **hyporeactive**. When a drug produces its effect at an unexpectedly low dosage, the patient is said to be **hyperreactive**. Some of this diversity in response rates can be attributed to differences in the rate of drug metabolism by the various cytochrome P450 enzymes.

For example, codeine, a pro-drug, is metabolized by demethylation into morphine, its active metabolite, by the cytochrome P450 isoenzyme CYP2D6.[21] Isoenzyme CYP2D6 is subject to genetic polymorphism. Up to 10% of patients are poor metabolizers of codeine and do not experience analgesia in response to treatment with codeine. Another 10% of the patients are rapid metabolizers of codeine, i.e., they rapidly convert codeine to morphine and may experience severe toxicity (including death), even with therapeutic doses.

Primary Oncogenesis-related ADRs

In general, drugs that cause direct damage to DNA and/or interfere with DNA repair are to be avoided in clinical practice. However, DNA damage and/or interference with DNA repair is the specific intent of cytotoxic alkylating agents used to treat neoplasia and such drugs can cause acute **myelocytic leukemia**.[1] Tamoxifen, an estrogen receptor antagonist used to treat estrogen-sensitive breast cancer, acting as a partial agonist at estrogen receptors in the uterus can cause **endometrial carcinoma**.[1]

Teratogenesis-related ADRs

Only a small number of drugs in clinical use have been positively implicated in teratogenesis. Of note for oral healthcare providers are the tetracyclines. They induce **enamel hypoplasia, discoloration of teeth, and diminished growth of long bones.**[22,23] Furthermore, they produce higher rates of **neuronal-tube defect, cleft palate**, and multiple congenital abnormalities such as **neuronal-tube defect with cardiovascular malformation**.[24]

Recent evidence suggests that acetaminophen (APAP) may interfere with neurodevelopment and children prenatally exposed to acetaminophen were more likely to develop autism spectrum and attention-deficit and hyperactivity symptoms[25,26] While the risk appears to be dose related, practitioners should prescribe APAP to pregnant patient only when necessary.[25,26]

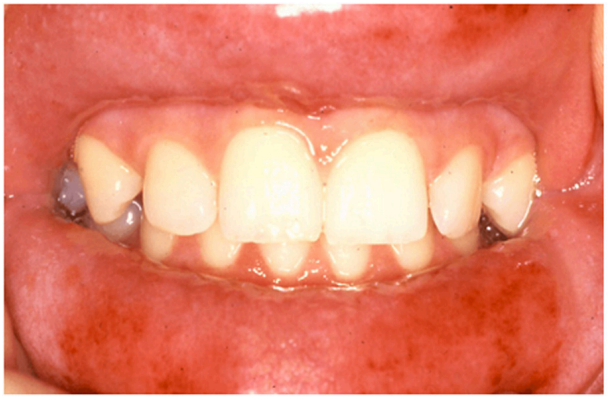


Figure 16. Type IV or Delayed Hypersensitivity Reaction in Response to a Cinnamon-flavored Sugar-free Gum.

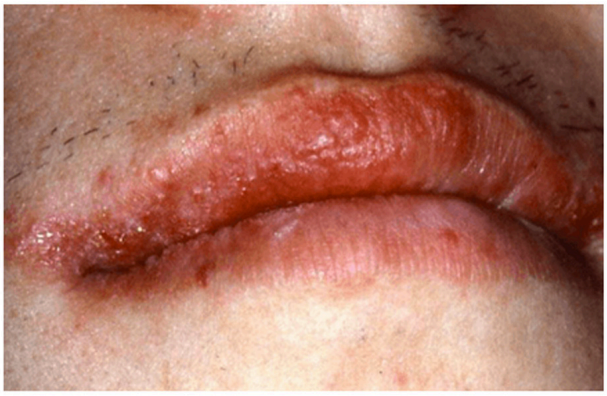


Figure 17. Type IV or Delayed Hypersensitivity Reaction in Response to an OTC Lip Balm Containing Benzocaine.

Secondary ADRs Related to Therapeutic Immunosuppression

Bacterial infections often contribute to morbidity and mortality associated with therapeutic immunosuppression.[16] A wide range of bacteria, including odontopathic, peri-odontopathic, and transient pathogens of the oral flora may manifest as ulcerative lesions. The normal signs of infection such as inflammation are not always obvious, with pain, fever, and the presence of a lesion observed most consistently (Figure 18).

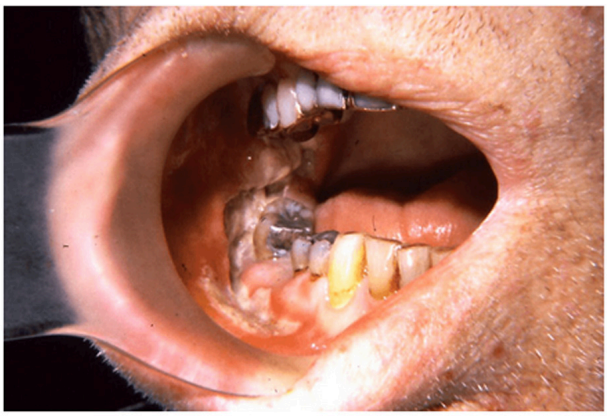


Figure 18. Coagulase-negative staphylococcal infection in a patient with leukemia undergoing chemotherapy.

Therapeutic immunosuppression is often complicated by **fungal infections** such as those associated with the *Candida* sp.[16] Oral candidiasis may present as white, raised, or cottage cheese-like growths that can be scraped off, leaving a red and sometimes hemorrhagic base. Via deglutition, droplet aspiration, or the hematological route oral candidiasis may spread to the esophagus or lungs; and, eventually, may affect all organ systems (Figures 19 and 20).

Viral infections in patients undergoing therapeutic immunosuppression include recurrent herpes simplex virus (HSV) infections affecting the lips and intraoral tissues (Figure 21).[16] The ulcerations are quite painful. The optimal period of observation for the detection of recurrent HSV infections is during the 7- to 14-day period following immunosuppression. Primary HSV infections account for less than 2% of infections in this patient population.

Herpes zoster (HZ) is a common clinical manifestation of immunosuppression-induced reactivation of the latent varicella zoster virus.[17] It is a localized, painful vesicular rash with an erythematous base restricted to skin and mucosal tissues and follows the distribution of a branch of the trigeminal nerve (Figures 22 and 23). Lesions are usually unilateral, deeper seated and more closely aggregated than those associated with chickenpox.

Epstein-Barr virus (EBV) infection has been associated with a wide range of syndromes in solid organ transplant recipients.[28] In the oral cavity, the EBV has been causally related to hairy leukoplakia, characteristically found on the lateral borders of the tongue in patients with therapeutic immunosuppression (Figure 24). As noted earlier, the EBV is an oncogenic virus, which when reactivated, may cause secondary malignancies.

Secondary malignancies related to therapeutic immunosuppression in susceptible individuals include de novo squamous cell carcinoma of the skin and lip (Figure 25).[29] Secondary malignancies related to immunosuppression-induced reactivation of oncogenic viruses include Kaposi sarcoma

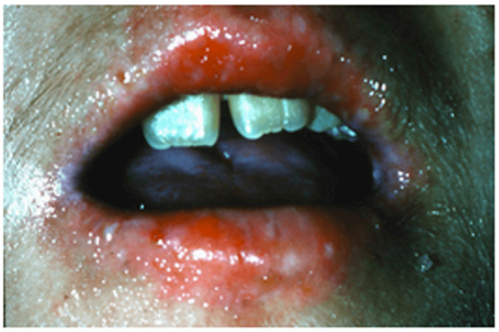


Figure 19.

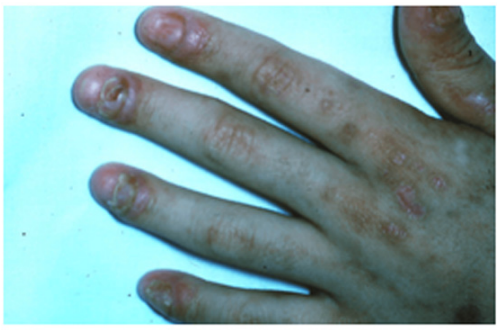


Figure 20.

Severe oral, dermal, and nail infection with candidal organisms in a patient undergoing immunosuppressive therapy prior to bone marrow transplantation.

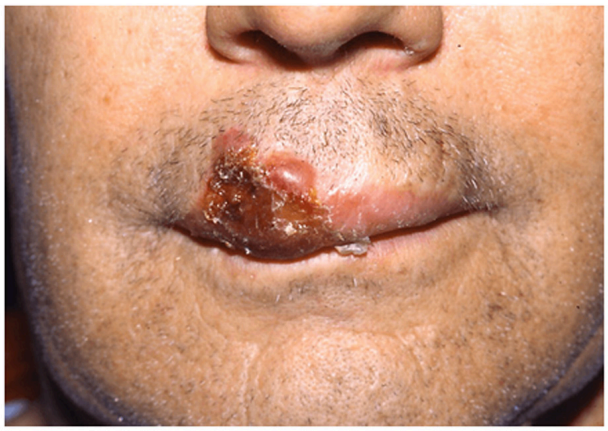


Figure 21. Atypical herpes labialis secondary to the reactivation of the latent HSV in a patient with leukemia undergoing chemotherapy.

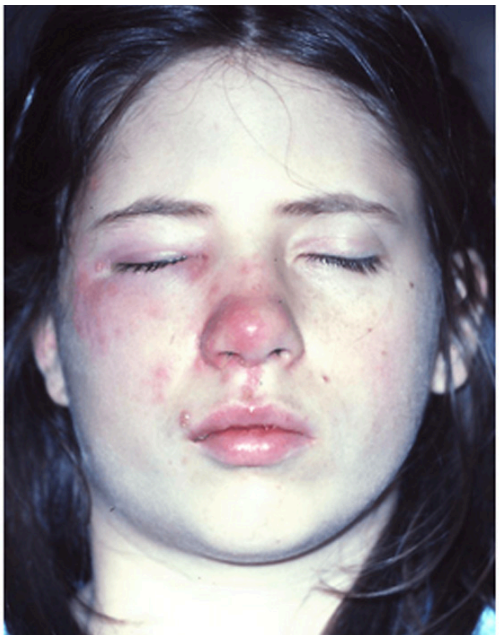
(Figure 26), lymphoproliferative diseases (Figure 27), Hodgkin's and non-Hodgkin's lymphomas, and spindle-cell sarcoma (Figure 28).[29]

Withdrawal Syndrome

Withdrawal syndrome is a substance-specific ADR associated with cessation or rapid reduction in the amount of a substance that an individual (usually a substance-dependent person) has been taking for a prolonged period of time and/or in high doses.[8] It results in clinically significant physiological or psychological distress or impairment in social, occupational or other important areas of functioning. It is most commonly associated with alcohol, tobacco, cocaine, amphetamines, and heroin addiction, and following the long-term use of therapeutic agents such as opioids and benzodiazepines. The signs and symptoms of withdrawal are specific to the specific agent withheld and commonly observed signs and symptoms are summarized in Table 2[30], but often include.

Preventing ADRs

Preventing ADRs is a critical part of clinical practice. Oral healthcare providers must be aware of and have access to information related to ADRs. To minimize ADRs, they must develop a rational approach when using pharmacotherapeutic agents to manage oral/odontogenic problems; especially, Whenever possible, definitive dental care should be accomplished to manage an oral/odontogenic



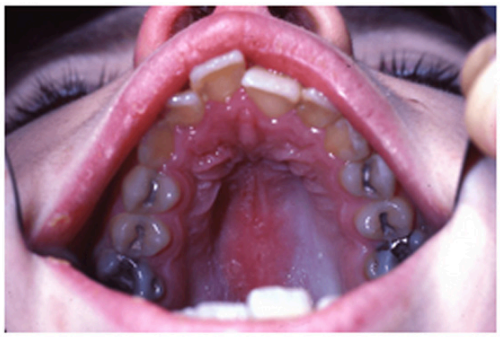


Figure 22 and 23. Herpes zoster infection involving the maxillary and ophthalmic divisions of the trigeminal nerve secondary to the reactivation of the latent VZV in a patient with leukemia undergoing chemotherapy.

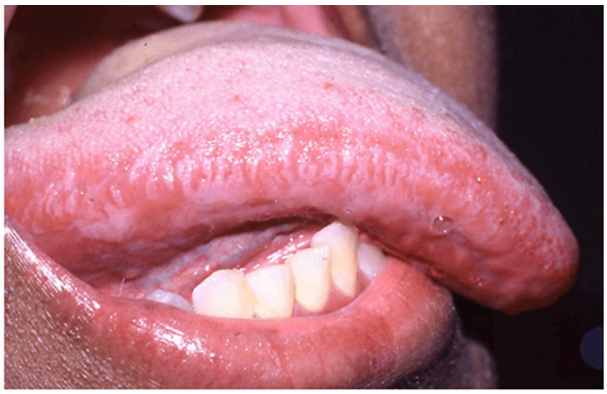


Figure 24. Hairy leukoplakia secondary to the reactivation of the latent EBV in a patient on therapeutic immunosuppression following renal transplantation.

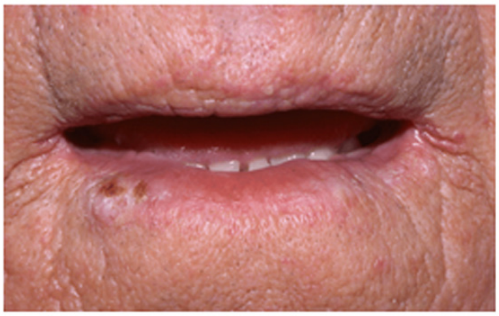


Figure 25. Squamous cell carcinoma of the lip in a patient 2 years after renal transplantation.

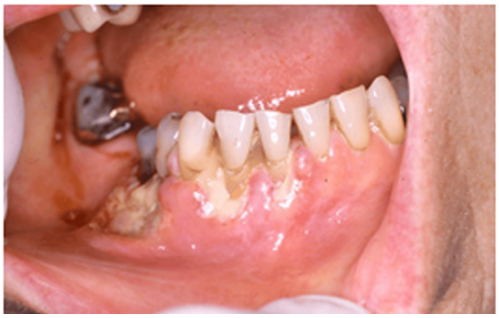


Figure 27. Epstein-Barr virus-related lymphoproliferative disease in a patient 3 years after renal transplantation.

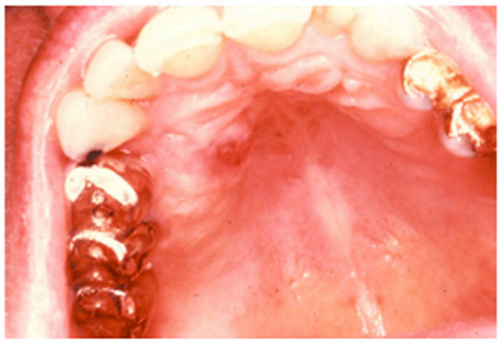


Figure 26. Human herpesvirus-8-related Kaposi sarcoma of the palate in a patient 4 years after renal transplantation.

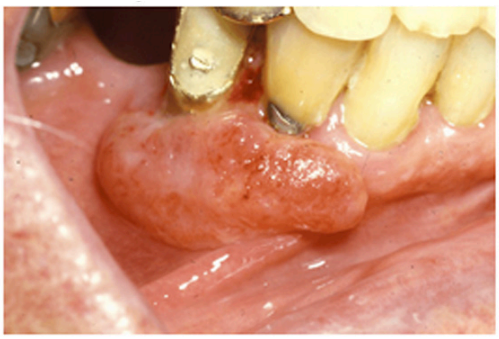


Figure 28. Epstein Barr virus-related spindle cell Sarcoma in a patient 4 years after renal transplantation.

problem. In most instances, definitive dental care is a more effective and safer alternative than pharmacotherapy.[31]

Inappropriate overprescribing is a significant concern in healthcare and practitioners must caution against prescribing out of convenience or to meet patient demand.[1,32-35] Overprescribing not only contributes to ADR risk but also to antimicrobial resistance and opioid habituation.

The benefit of use should always outweigh the risks when a drug is prescribed. If clinicians were to observe this basic principle routinely, the number of unnecessary or inappropriate prescriptions would be reduced. Drug therapy should be individualized by taking into consideration both drug- and patient-related variables.[36-38] Patient-related factors that contribute to ADR risk include progressing age, multiple co-morbidities, living alone, and poor coping skills of ambulatory patients.

When a medication is prescribed, the patient and/or guardian/caretaker must have a clear understanding of its purpose and dosing. Simple and clear oral instructions on how and when to take a drug should be given and reinforced by clear labeling and written instructions. Special labels are available for blind or poorly sighted patients.

Follow-up should be accomplished to assess the patient's compliance and response to drug therapy. The patient should be encouraged to report any potential ADR so that appropriate action can be taken, e.g., dosage adjustments or discontinuance of medication. Complex regimens and frequent dosing lend themselves to noncompliance. A byproduct of poor compliance is hoarding of drugs, which can further contribute to noncompliance and ADRs as patients may confuse new bottles with old ones or use hoarded drugs for the wrong purpose.

Diagnosing ADRs

The diagnosis of ADRs is highly subjective and imprecise. Complaints such as fatigue, inability to concentrate, and excessive sleepiness have been reported by healthy individuals not taking medications. It is also well known that patients receiving a placebo report ADRs. However, drugs

Table 2. Common Signs & Symptoms of Drug Withdrawal[29]		
Trembling and tremors	Muscle pain or aches	Hunger or loss of appetite
Fatigue	Sweating	Irritability and agitation
Depression	Anxiety	Nausea
Vomiting	Confusion	Insomnia
Paranoia	Seizures	Dilated pupils

as disease and symptom producing agents should always be considered when formulating a differential diagnosis. The following step-wise process can be used to identify possible drug-related adverse reactions:

- Step 1 – Identify the drug(s) taken by the patient.
- Step 2 – Verify that the onset of signs and symptoms was after the initiation of pharmacological intervention.
- Step 3 – Determine the time-interval between the initiation of drug therapy and the onset of signs and symptoms.
- Step 4 – Stop drug therapy and monitor signs and symptoms.
- Step 5 – In rare instances it may be appropriate to restart drug therapy and monitor for recurrence of signs and symptoms.

Reporting ADRs

The FDA is responsible for ensuring the safety of all marketed drugs; and, consequently, for maintaining a post-marketing surveillance program to identify ADRs. The success of this program depends on active participation by all clinicians. The FDA launched **MedWatch**, an initiative designed to educate health care professionals about the critical importance of being aware of, monitoring for, and reporting ADRs.[39]

It is important to note that the reporting clinician is not responsible for proving causality; a suspected association constitutes sufficient reason to report. The FDA holds the identity of the patient in strict confidence. However, unless otherwise indicated on the reporting form, the reporting clinician's identity may be shared with the drug manufacturer. Reports may be sent directly to the FDA by several different mechanisms:

- *View Form FDA 3500 Instructions*
  - *Complete voluntary Form FDA 3500 online*
  - Call 1-800-FDA-1088 to report by telephone
  - *Download form* or call 1-800-332-1088 to request a reporting form
    - Complete and return the form to the address on the pre-addressed form, OR
    - Submit the form by fax to 1-800-FDA-0178

Based on these reports, the FDA may send out "Dear Health Professional" letters; require warning labels and/or changes to the packaging information (package insert); request further epidemiological investigations and/or manufacturer-sponsored post-marketing studies; and conduct inspections of manufacturers' facilities and/or records. Ultimately, the FDA may require the drug's withdrawal from the market.

Summary

In considering ADRs in the differential diagnosis of a patient's problem, the practitioner must acknowledge that there are no "absolutely safe" medications and be familiar with relevant literature about ADRs. It is equally important to recognize that some ADRs occur sporadically and detection based on clinical experience or reports in the literature is lacking. Improved reporting of ADRs should save lives, reduce morbidity, and decrease the cost of healthcare.

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: *www.dentalcare.com/en-us/ce-courses/ce537/start-test*

1. Major categories of ADRs related to the immune system include all of the following, EXCEPT for one. Which one is the exception?

A. immunotoxicity
B. autoimmune reactions
C. hypersensitivity or allergic reactions
D. Habituation

2. All of the following statements related to autoimmune reactions are correct, EXCEPT for one. Which one is the exception? An autoimmune reaction may _____.

A. be the specific intent of therapy, e.g., when monoclonal antibodies target specific B cells
B. elicit an antibody response to Rh factors on red blood cells (RBCs) causing hemolytic anemia
C. induce an antibody response to myeloperoxidase or DNA causing a lupus-like syndrome
D. directly cause mast cell degranulation resulting in urticarial lesions

3. All of the following statements related to hypersensitivity or allergic reactions are correct, EXCEPT for one. Which one is the exception?

A. Therapeutic peptides or proteins with molecular weights >600 daltons are recognized by the immune system as foreign substances and can directly trigger allergic reactions.
B. Drugs with molecular weights <600 daltons are too small to act as direct immunogens; however, these drugs may act as haptens.
C. The Gell-Coombs classification system consists of five mechanisms of hypersensitivity or allergic reactions.
D. An allergic response is predicated on sensitization, i.e., prior exposure to a drug.

4. All of the following statements related to Type I or immediate hypersensitivity reactions (anaphylaxis) are incorrect, EXCEPT for one. Which one is the exception?

A. Type I reactions are predicated on exposure to an allergen and antigen-specific antibody production dominated by immunoglobulin E (IgE) isotype.
B. Type I reactions are predicated on exposure to an allergen and antigen-specific antibody production dominated by immunoglobulin G (IgG) or M (IgM) isotypes.
C. Type I reactions are predicated on exposure to haptens, which bind to endogenous macromolecules and form hapten-protein complexes.
D. In Type I reactions Langerhans cells phagocytize and process hapten-protein complexes, load them into major histocompatibility complexes, migrate to regional lymph nodes and present them to naïve T-lymphocyte.

5. All of the following statements related to Type IV or delayed T-cell mediated hypersensitivity reactions are incorrect, EXCEPT for one. Which one is the exception? Upon re-exposure to a specific antigen, _____.

A. IgE antibodies bind to mast cells in mucosal and epithelial tissues and trigger degranulation of mast cells resulting in the production and release of histamine, leukotrienes, prostaglandins, and cytokines
B. the antigen binds to the surface of target cells (usually RBCs), the antigen-antibody complexes attract cytotoxic T cells, which release chemical mediators that cause target-cell lysis
C. soluble drug molecules form large insoluble antigen-antibody complexes that are deposited in target tissues (e.g., kidneys, joints and lungs) and initiate complement activation, neutrophil and platelet aggregation, and an intense inflammatory response
D. sensitized T cells in target tissues activate macrophages, which mediate direct cellular damage

6. All of the following statements related to idiosyncratic ADRs are incorrect, EXCEPT for one. Which one is the exception?

A. Idiosyncratic ADRs are observed in a small number of patients.
B. Idiosyncratic ADRS are predictable.
C. Factors influencing drug response phenotype include age, gender, underlying disease, and genetic and epigenetic mechanisms.
D. Genetic polymorphism and epigenetic factors have been implicated in both pharmacokinetic and pharmacodynamic variations.

7. All of the following statements related to oncogenic mechanisms of ADRs are correct, EXCEPT for one. Which one is the exception?

A. Primary oncogenic effects can be produced by drugs that damage DNA or by drugs that facilitate proliferation of cells carrying precancerous mutations.
B. Oncogenes are proto-oncogenes, which through amplification or mutation became permanently activated allowing abnormal cells to proliferate.
C. Inactivated tumor suppressor genes slow down cell division, promote the repair of damaged DNA, and initiate apoptosis.
D. Secondary oncogenic effects are related to therapeutic immunosuppression-induced reactivation of latent oncogenic viruses.

8. All of the following statements related to teratogenesis are correct, EXCEPT for one. Which one is the exception?

A. Teratogenesis is the process that results in structural and/or functional defects in a fetus.
B. Exposure to a teratogen during organogenesis, i.e., from day 18 to day 55 results in developmental abnormalities.
C. The period from day 55 through the 3rd trimester is a period of fetal growth, exposure to a teratogen affects organ function.
D. Teratogens present the greatest risk to the embryo during periods of subdued mitotic acitivity.

9. All of the following statements related to rash or pruritus are correct, EXCEPT for one. Which one is the exception?

A. Rash is a specific term and its use is encouraged in describing an ADR characterized by skin eruption.
B. Pruritus may be a symptom of primary skin lesions or less frequently that of a systemic disease.
C. Pruritus may be the result of drug-induced histamine release by mast cells unrelated to the immune system.
D. Pruritus may reflect a bona fide drug-related allergic reaction.

10. All of the following ADRs are likely to be unrelated to IgE-induced mast cell degranulation and be described as an anaphylactoid or pseudoallergic reaction, EXCEPT for one. Which one is the exception?

A. Opioid analgesic-induced central pruritic action and peripheral histamine release.
B. Vancomycin and ciprofloxacin-induced red man syndrome characterized by itching followed by the emergence of a “rash” or hives, i.e., urticaria.
C. Some cases of NSAID-, penicillin-, and antifungal agent-induced itching and urticaria.
D. Type III immune reactions, such as serum sickness.

11. All of the following statements related to urticaria are correct, EXCEPT for one. Which one is the exception?

A. Urticaria is a well-circumscribed erythematous, pruritic plaque on skin associated with the release of histamine and other vasoactive substances from mast cells and basophils resulting in intradermal edema caused by vasodilation.
B. A rare feature of urticaria is subcutaneous and submucosal angioedema of target tissues.
C. Chronic urticaria is usually idiopathic or it may be associated with auto-antibodies to IgE receptors causing mast cell degranulation.
D. Acute urticaria most often reflects a hypersensitivity or allergic reaction in which allergen-bound IgE initiates mast cell and basophil degranulation.

12. All of the following statements related to angioedema are correct, EXCEPT for one. Which one is the exception?

A. Acute angioedema (< 6 weeks) is bradykinin-mediated in >90% of cases.
B. Chronic angioedema is rarely IgE-mediated; it is usually idiopathic and may be caused by the chronic ingestion of certain drugs (e.g., penicillin), preservatives, milk, and food additives; and a few cases are hereditary.
C. While it may be localized, swelling of the extremities, face, lips, tongue, oropharynx, and larynx along with stridor, wheezing, and hypotension are harbingers of anaphylaxis.
D. Bradykinin mediated angioedema may occur soon or years after ACE inhibitor therapy initiation.

13. All of the following statements related to erythema multiforme (EM) are correct, EXCEPT for one. Which one is the exception?

A. EM is an acute T cell-mediated cytolytic reaction.
B. The majority of EM cases are drug-induced related to NSAIDs, penicillins, anticonvulsants, and sulfonamides.
C. Cutaneous lesions begin as erythematous papules that progress to form the more characteristic iris or target lesions.
D. Hemorrhagic crusting of the lips and vesiculoerosive lesions on unattached oral mucosal tissues are considered pathognomonic.

14. All of the following statements related to EM, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) are correct, EXCEPT for one. Which one is the exception?

A. SJS and TEN are considered to be separate entities from EM.
B. The majority of SJS and TEN cases are associated with the herpes simplex virus.
C. Oral features of SJS and TEN are similar to those associated with EM.
D. The major difference between SJS and TEN is the distribution of dermal lesions: SJS affects <10% of the body surface while TEN affects >30%.

15. All of the following statements related to lichenoid reactions are correct, EXCEPT for one. Which one is the exception?

A. Drugs such as NSAID's and ACE inhibitors can act as haptens and alter the antigenicity of epithelial self-antigens.
B. Oral lichen planus that can be traced to an extrinsic cause is more properly termed a lichenoid reaction.
C. Oral lichenoid lesions may be "reticular", atrophic, or erosive.
D. Oral lichenoid most often affect the palate.

16. All of the following statements related to arthralgia are correct, EXCEPT for one. Which one is the exception?

A. Drugs associated with arthralgia include antimicrobials, anti-mycobacterials, antifungals, antidiabetic, chemotherapeutics, retinoids, cytokines, and psychotropics.
B. The most common cause of arthralgia is arthritis; other causes include injury and infection.
C. A single unifying mechanism of action has been determined to explain ADR-related arthralgia.
D. Arthralgia is the 24th most commonly reported ADR associated with the top 200 drugs.

17. All of the following statements related to Type I hypersensitivity reactions are correct, EXCEPT for one. Which one is the exception?

A. Anaphylaxis occurs within minutes to hours after parenteral or enteral administration of a drug in a previously sensitized patient.
B. The longer the reaction time to an antigen, the more severe the anaphylactic reaction is.
C. Skin-related signs and symptoms of anaphylaxis include erythema, urticaria, and angioedema.
D. Cardiopulmonary effects of anaphylaxis include bronchospasm, hypotension, and shock.

18. All of the following statements related to either a Type II or Type III hypersensitivity reaction are correct, EXCEPT for one. Which one is the exception?

A. The time required for cytotoxic T cell-mediated target cell lysis or for target cell lysis mediated by the complement system in response to a specific antigen is 1 to 3 weeks.
B. Clinical manifestations of Type II antibody-dependent cytotoxic reactions include hemolytic anemia, neutropenia, and thrombocytopenia.
C. Serum sickness-like reactions clinically similar to serum sickness have been noted in association with non-protein drugs such as penicillins, cephalosporins, sufonamides, bupropion, fluoxetine, and thiouracil.
D. Common symptoms of serum sickness include fever, cutaneous eruptions (usually urticaria), arthralgia, gastrointestinal complains (nausea, vomiting, diarrhea, or abdominal pain), headaches, myalgia, dyspnea and wheezing, and lymphadenopathy.

19. All of the following statements related to Type IV hypersensitivity or delayed T cell-mediated reactions are correct, EXCEPT for one. Which is the exception?

A. Type IV hypersensitivity reactions are mediated by immunologically committed plasma cells.
B. In susceptible patients, cytokines and other mediators of inflammation are released within 2 to 7 days of re-exposure to an allergen.
C. Clinical manifestations include allergic contact dermatitis/mucositis or a drug-induced maculopapular rash.
D. With repeated antigenic challenge, the response becomes more profound and includes fever, malaise, and angioedema in target tissues.

20. All of the following statements related to idiosyncratic ADRs are correct, EXCEPT for one. Which one is the exception?

A. Idiosyncrasy is an unpredictable reaction of any intensity observed in a small number of the individuals.
B. When a drug produces its usual effect on a person at an unexpectedly high dose, the patient is said to be hyperreactive.
C. Because of genetic polymorphism, up to 10% of patients are poor metabolizers of codeine and do not experience analgesia in response to treatment with codeine.
D. Because of genetic polymorphism, up to 10% of patients are rapid metabolizers of codeine and may experience severe toxicity even with therapeutic doses.

21. All of the following statements related to primary oncogenesis-related ADRs is correct, EXCEPT for one. Which one is the exception?

A. In general, drugs that cause direct damage to DNA and/or that interfere with DNA repair are avoided in clinical practice.
B. DNA damage and/or interference with DNA repair is the specific intent of cytotoxic alkylating agents used to treat neoplasia and such drugs can cause acute myelocytic leukemia.
C. Tamoxifen, an estrogen receptor antagonist used to treat estrogen-sensitive breast cancer, acting as a partial agonist at estrogen receptors in the uterus can cause endometrial carcinoma.
D. Tamoxifen, an estrogen receptor antagonist used to treat estrogen-sensitive breast cancer, acting as a partial agonist at estrogen receptors in the uterus has been shown to decrease the risk of endometrial carcinoma.

22. All of the following statements related to teratogenesis-related ADRs are correct, EXCEPT for one. Which one is the exception?

A. A large number of drugs in clinical use have been positively implicated in teratogenesis.
B. Tetracyclines induce enamel hypoplasia, discoloration of teeth, and diminished growth of long bones.
C. Tetracyclines produce higher rates of neuronal-tube defect, cleft palate, and multiple congenital abnormalities such as neuronal-tube defect with cardiovascular malformation.
D. Recent evidence suggests that acetaminophen (APAP) may interfere with neurodevelopment and children prenatally exposed to acetaminophen were more likely acetaminophen (APAP) to develop autism spectrum and attention deficit and hyperactivity symptoms.

23. All of the following statements related to therapeutic immunosuppression-induced secondary ADRs are correct, EXCEPT for one. Which one is the exception?

A. Bacterial infections often contribute to morbidity and mortality associated with therapeutic immunosuppression.
B. Therapeutic immunosuppression is often complicated by fungal infections such as those associated with the Candida sp.
C. Common viral infections in patients undergoing therapeutic immunosuppression include primary HSV infections.
D. Herpes zoster (HZ) is a common clinical manifestation of immunosuppression-induced reactivation of the latent varicella zoster virus.

24. All of the following statements related to therapeutic immunosuppression-induced secondary malignancies are correct, EXCEPT for one. Which one is the exception?

A. Secondary malignancies related to therapeutic immunosuppression in susceptible individuals include de novo squamous cell carcinoma of the skin.
B. Secondary malignancies related to therapeutic immunosuppression in susceptible individuals include de novo squamous cell carcinoma of the lip.
C. Secondary malignancies related to immunosuppression-induced reactivation of oncogenic viruses include hepatocellular carcinoma and cervical cancer.
D. Secondary malignancies related to immunosuppression-induced reactivation of oncogenic viruses include Kaposi sarcoma, lymphoproliferative diseases, Hodgkin's and non-Hodgkin's lymphomas, and spindle-cell sarcoma.

25. All of the following statements related to withdrawal syndrome are correct, EXCEPT for one. Which one is the exception?

A. Withdrawal syndrome is a substance-specific ADR associated with cessation or rapid reduction in the amount of a substance that an individual has been taking for a prolonged period of time and/or in high doses.
B. Withdrawal syndrome results in clinically significant physiological or psychological distress or impairment in social, occupational or other important areas of functioning.
C. Withdrawal syndrome is most commonly associated with alcohol, tobacco, cocaine, amphetamines, and heroin addiction; and following the long-term use of therapeutic agents such as opioids and benzodiazepines.
D. The signs and symptoms of withdrawal syndrome are the same, regardless of the agent withdrawn.

26. All of the following statements related to preventing ADRs are correct, EXCEPT for one. Which one is the exception?

A. Preventing ADRs is a critical part of clinical practice.
B. In the treatment of most oral/odontogenic problems non-pharmacological intervention, i.e., primary dental care is more effective and a safer alternative to pharmacotherapy.
C. When pharmacotherapy is indicated practitioners must embrace patient demand.
D. Inappropriate overprescribing is a major concern in healthcare.

27. All of the following statements related to preventing ADRs are correct, EXCEPT for one. Which one is the exception?

A. Overprescribing does contribute to ADR risk, but not to antimicrobial resistance and opioid habituation.
B. The benefits should always outweigh the risks when a drug is prescribed.
C. Drug therapy should be individualized by taking into consideration both drug- and patient-related variables.Simple and clear oral instructions on how and when to take a drug should be given and reinforced by clear labeling and written instructions.
D. Patient-related factors that contribute to ADR risk include progressing age, the presence of multiple co-morbidities, living alone, and poor coping skills.

28. All of the following statements (steps) related to diagnosing ADRs are correct, EXCEPT for one. Which one is the exception?

A. Identify the drug(s) taken by the patient and verify that the onset of signs and symptoms was after the initiation of pharmacological intervention.
B. Determine the time-interval between the initiation of drug therapy and the onset of signs and symptoms.
C. Stop drug therapy and monitor signs and symptoms.
D. Once the ADR is resolved, it is good practice to restart drug therapy to confirm causality.

29. All of the following statements related to reporting ADRs are correct, EXCEPT for one. Which one is the exception?

A. The FDA launched MedWatch, an initiative designed to educate health care professional about the critical importance of being aware of, monitoring for, and reporting ADRs.
B. The reporting clinician is not responsible for proving causality; a suspected association constitutes sufficient reason to report.
C. The FDA holds the identity of the patient in strict confidence.
D. The reporting clinician's identity must be shared with the manufacturer of the drug.

30. All of the following statements related to the FDA's response to reports of ADRs are correct, EXCEPT for one. Which one is the exception?

A. The FDA may send out "Dear Health Professional" letters and require warning labels and/or changes to the packaging information (package insert).

B. The FDA may request further epidemiological investigations and/or manufacturer-sponsored post-marketing studies and conduct inspections of manufacturers' facilities and/or records.

C. The FDA may impose a financial penalty on the manufacturer.

D. The FDA may require withdrawal of the drug from the market.

References / Additional Resources

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Additional Resources

No Additional Resources Available

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