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# PART 1: Executive Summary of Disease Management of Drug Hypersensitivity: A Practice Parameter

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Adverse drug reactions are a major health problem in the United States. About 25% of all adverse drug reactions have an allergic, pseudoallergic, or idiosyncratic/intolerant basis. Idiosyncratic drug reactions and drug intolerance are also included in this category. Drug allergy may be classified by the Gell and Coombs classification of human hypersensitivity (Type 1: IgE-mediated; Type 2: cytotoxic; Type 3: immune complex; and Type 4: cellular immune mediated). Drug allergy is also frequently characterized by the predominant tissue/organ involved (systemic, cutaneous, or visceral). To some extent, the structural characteristics of drugs and biologic products predict the type of hypersensitivity reaction.

The most important risk factors for drug hypersensitivity are related to the chemical properties and molecular weight of the drug. Other drug-specific risk factors include the dose, route of administration, duration of treatment, repetitive exposure to the drug, and concurrent illnesses. Host risk factors include age, gender, atopy, and specific genetic polymorphisms.

The history, physical examination, and objective clinical and laboratory tests are important components in the clinical evaluation and diagnosis of drug hypersensitivity. The history should focus on such items as previous and current drug use, the toxicity/allergenicity of previously and currently used drugs, the temporal sequence of events between initiation of therapy, and onset of symptoms. Physical examination should include all systems that could possibly account for the clinical presentation. Possible clinical tests might include but are not limited to a chest x-ray, electrocardiogram, a

complete blood count with differential, sedimentation rate, nuclear and cytoplasmic autoantibody tests, and specific immunologic tests. The most useful test for detecting IgE-mediated drug reactions caused by many large molecular weight biologicals and penicillin is the immediate hypersensitivity skin test. Patch testing is the most reliable technique for diagnosis of contact dermatitis caused by topically applied drugs.

Anaphylactic drug reactions require prompt emergency treatment, which consists of: (1) oxygen; (2) maintenance of the airway; (3) IM or SC epinephrine [adults, 0.2 to 0.5 mL of a 1:1000 (1 mg/mL, wt/vol) dilution every 10 to 15 minutes up to a maximum dose of 1.0 mL per dose; children, 0.01 mL (0.01 mg)/kg body weight up to a maximum of 0.5 mL per dose of a 1:1000 dilution, repeated every 15 minutes for 2 doses, then every 4 hours as needed]; (4) parenteral diphenhydramine (1 to 2 mg/kg or 25 to 50 mg); (5) intravenous hydrocortisone, primarily for a late response; (6) intravenous fluids and vasopressors for hypotension; and (7) CPR as needed. This emergency regimen is discussed extensively in "Practice Parameters for the Diagnosis and Treatment of Anaphylaxis" (*J Allergy Clin Immunol* 1998; 101:S484). For mild drug reactions, withdrawal of the drug may be all that is required. Glucocorticosteroids may be required to speed recovery from immune complex and cytotoxic drug reactions. In sensitive patients who require the drug that caused the adverse reaction, rapid desensitization may be necessary when alternative drugs cannot be substituted for anaphylactogenic ones. Slower graded challenge regi-

mens may be utilized for drugs associated with a variety of non-IgE-mediated hypersensitivity reactions. The principles of preventing allergic drug reactions include (1) a careful history to determine host risk factors, (2) avoidance of drugs that have caused previous reactions, (3) avoidance of cross-reactive drugs, (4) use of predictive tests when available, (5) prudent prescribing of drugs frequently associated with adverse drug reactions, and (6) use of oral as opposed to parenteral drugs.

Many drugs are known to induce anaphylaxis. These have been discussed more extensively in "Practice Parameters for the Diagnosis and Treatment of Anaphylaxis" (*J Allergy Clin Immunol* 1998;101:S498-S516). The major prototypes of IgE-mediated anaphylactic reactions are  $\beta$ -lactam antibiotics. Penicillin and its analogs are the most frequent cause of allergic drug reactions in the United States. Both negative and positive predictors of an immediate hypersensitivity reaction can be obtained by properly performed skin tests to penicillin using major (penicilloyl) and minor determinants (minor determinant mixtures or penicillin-G) of penicillin. In the event that skin tests are positive to these reagents and the patient requires an antibiotic for which there is no acceptable substitute, desensitization is indicated. Carbapenams are cross-reactive with penicillin. Although the monobactam, aztreonam, is structurally similar to penicillin, clinical reactions to this drug in penicillin-sensitive patients are rare. Varying degrees of cross-reactivity between cephalosporins and penicillins have been documented. First generation cephalospo-

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rins may pose a greater risk for penicillin cross-reactivity than second or third generation cephalosporins. Skin testing for cephalosporin hypersensitivity is not standardized as it is for penicillin. The overall incidence of hypersensitivity reactions to non- $\beta$ -lactam antibiotics ranges from 1% to 3%. Although rare, IgE-mediated anaphylaxis may occur after administration of any non- $\beta$ -lactam antibiotic (eg, vancomycin, aminoglycosides, and fluorinated quinolones).

Gell-Coombs immunocytotoxic Type 2 reactions are serious and potentially life-threatening. Immuno-hemolytic anemias may occur after treatment with quinidine,  $\alpha$ -methyl dopa and penicillin, among others. Immune-induced thrombocytopenia and granulocytopenia may be induced by a variety of drugs.

Gell-Coombs immune complex Type 3 reactions may occur after use of heterologous antisera, murine monoclonal antibodies, and some small molecular weight drugs such as penicillin. The immunopathogenesis of these reactions involves IgG and/or IgM immune complexes and in some cases IgE antibodies. Treatment consists of H<sub>1</sub> blockers and in severe cases, high dose glucocorticosteroids.

Drugs may also induce Gell-Coombs cell-mediated Type 4 immune reactions. Contact dermatitis due to topical drugs and/or excipients is the most common example of this type of reaction. Patch testing at proper concentrations is often successful in detection of suspected or unsuspected contactant allergens. After avoidance is instituted, topical and/or systemic glucocorticosteroids may be required for total clearing of the dermatitis. Some

cutaneous allergic drug reactions (morbilliform rashes, eczematous rashes, erythroderma, exfoliative dermatitis, and mucocutaneous blistering disorders) cannot be classified within the Gell-Coombs paradigm. Immunopathogenesis is suspected, however, because a number of these reactions are associated with CD4<sup>+</sup>/CD8<sup>+</sup> positive T cells, drug specific T cell clones and in some cases, positive patch tests.

Specific drugs may be associated with characteristic syndromes which do not conform with typical presentations defined by the Gell-Coombs classification of human hypersensitivity. Some drugs may induce vasculitides of the skin and visceral organs with clinical syndromes resembling lupus erythematosus or systemic granulomatous vasculitis, the Churg-Strauss syndrome. Anti-convulsive medications may cause a life-threatening systemic hypersensitivity reaction characterized by pseudolymphoma and diffuse inflammation of the liver and kidney. Hypersensitivity drug reactions in the lung may cause alveolar or interstitial pneumonitis, edema, granulomatosis, and fibrosis. Drugs such as sulfonamides and anti-convulsive agents can be associated with life-threatening blistering mucocutaneous disorders such as the erythema multiforme major/Stevens-Johnson syndrome and toxic epidermal necrolysis. Cancer chemotherapeutic agents such as L-asparaginase, doxorubicin, and cisplatin may be associated with IgE-mediated anaphylaxis. A variety of drugs commonly used during the operative and perioperative periods (eg, protamine, heparin and muscle relaxants) may cause anaphylaxis or delayed hyper-

sensitivity responses. Most adverse reactions to local anesthetics are not allergic in etiology and often present as vasovagal responses.

Opiates, radiocontrast media (RCM), colloid volume substitutes and Cremophor-EL are among the substances that may cause pseudoallergic reactions. A unique group of non-immune idiosyncrasy/intolerance syndromes may be induced by aspirin (ASA), other nonsteroidal anti-inflammatory agents (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and several excipient preservatives. These reactions can be life-threatening. Special regimens are available for prevention of some of these reactions (eg, RCM reactions, dextran) or desensitization for ASA/NSAIDs.

Drug reactions are common in patients with AIDS and in some cases, the incidence of reactions may be related to the degree of immunodeficiency. Adverse reactions to sulfonamides and trimethoprim-sulfamethoxazole (TMP-SMX) are frequently encountered in patients with AIDS. In addition to sulfonamides, there is an increased frequency of adverse reactions to anti-mycobacterial agents, pentamidine, phenytoin, zidovudine and other medications. In patients who develop late onset morbilliform rashes after TMP-SMX administration, several desensitization or graded challenge protocols have been developed and successfully implemented. Rechallenge is contraindicated in any patient with a history of a mucocutaneous bullous dermatitis associated with the drug. Sulfadiazine, acyclovir and zidovudine graded challenge protocols have also been described for patients with AIDS.

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# Annotations of the Algorithm for Disease Management of Drug Hypersensitivity

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## **\*ANNOTATION 1: Patient develops a possible adverse drug reaction**

Adverse drug reactions (ADR) encompass a wide range of clinical symptoms and signs that may be confused with a preexistent disease, a proximate unexpected clinical event (eg, drug-induced liver disease versus viral hepatitis) or a disorder that would not have occurred if the drug had not been used (eg, aseptic necrosis after large doses of glucocorticosteroids). As defined by the World Health Organization, such reactions do not include therapeutic failures, intentional overdose, abuse of the drug, or errors in administration. Adverse drug reactions occur more frequently in seriously ill patients requiring multiple drugs, alcoholics, patients with HIV infection/AIDS, or underlying hepatic or renal impairment. Occasionally, the occurrence of an unexpected event during drug administration may be mistakenly attributed to extension of the underlying disease rather than to the drug itself. In certain instances, there may be an excessive reaction to the primary effect of the drug (eg, diarrhea after a laxative). Very serious side effects such as birth defects or malignancies may occur long after drug exposure has ceased. In making a determination about whether the patient is experiencing an ADR, the physician must appreciate the wide scope of such reactions with special emphasis on early recognition, pathophysiologic mechanisms, and severity. In addition, pharmacologic-based ADR often are dose-dependent while idiosyncratic, intolerant, and hypersensitivity responses may be elicited by relatively small doses.

Serious adverse drug reactions are a major health problem in the United States and are estimated to cause between 75,000 and 106,000 deaths per year. The majority of adverse drug reactions are (1) expected pharmacologic side effects; (2) drug-drug interactions; (3) pharmacogenetic abnormalities (ie, altered drug biotransformation pathways); (4) drug/disease specific events (eg, ampicillin-induced rash, especially in acute Epstein-Barr infection); (5) alterations of tissue ecology (overgrowth of *Candida* in patients receiving antibiotics or glucocorticosteroids); or (6) secondary pharmacologic effects of the drug (eg, aspirin-induced gastrointestinal hemorrhage).

The proportion of all adverse drug reactions that can be ascribed to idiosyncratic/intolerance reactions, pseudoallergy, or drug hypersensitivity is about 25%. Whereas drug idiosyncrasy/intolerance and pseudoallergic reactions, as defined in the glossary, are non-immune reactions, drug hypersensitivity is defined as a specific immunologic reaction to a drug in a sensitized patient. Skin rashes, angioedema, wheezing, or anaphylaxis are the most common presentations for drug allergy.

In assessing the possibility of an adverse drug reaction, knowledge about the dose, duration of usage, temporal relationship of drug administration and predilection of drugs for specific organs or tissues is important. In addition, the chemical structure of drugs may provide useful clues about the type of hypersensitivity that is most likely to occur. Attention to these factors usually can distinguish pseudoallergic reactions, which occur as a result of mediator release from mast cells or basophils without a prior sensitization period, from specific immunologically mediated drug hypersensitivity reactions.

## **\*ANNOTATION 2: Review of medical history, the patient's records, physical examination and clinical tests support an adverse drug reaction**

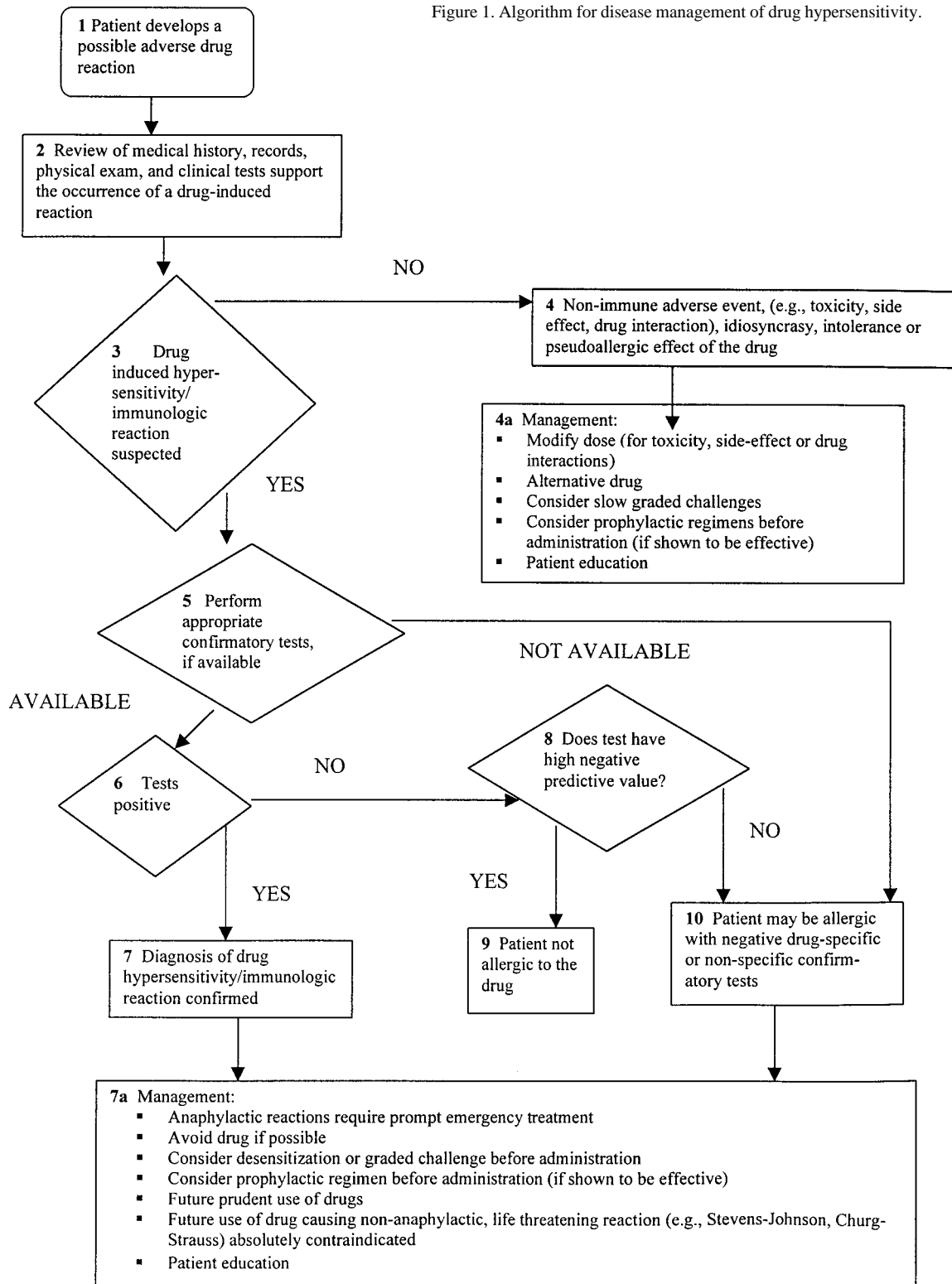
A careful history, including a review of any available medical records, is essential. The history should include (1) timing of the onset, course, and duration of symptoms; (2) a description of symptoms with special attention to the organ system(s) involved; (3) the possible temporal relationship of symptoms with medication use; (4) a detailed list and description of all medications, both prescription and non-prescription that the patient is taking including dose, dosing interval and length of treatment; (5) a detailed history of previously suspected drug reactions; and (6) a description of the management of previous drug reactions and measures taken to prevent recurrence of such reactions. A review of available medical records will help to confirm the patient's medication history and may provide details about previously suspected drug reactions, including the treatment of these reactions. Host risk factors obtained from the history, such as age, gender, and genetic associations [eg, atopy (usually for reactions to high molecular weight biologicals), familial, genetic polymorphisms of HLA-DR and various drug metabolizing enzymes] may support the possibility of a hypersensitivity drug reaction.

Since adverse drug reactions may involve any organ system, a complete physical examination is recommended in any patient who presents with a possible adverse reaction to a drug. Based on the history and physical examination, laboratory tests, including differential, blood chemistries, such as liver or renal function tests, a chest x-ray, and/or an electrocardiogram may be advisable. Specific tests which may

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\*See algorithm in Figure 1, on page 668.

Figure 1. Algorithm for disease management of drug hypersensitivity.



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help to define immunopathogenesis are described in ANNOTATIONS 5–11.

**\*ANNOTATION 3: Drug-induced hypersensitivity/immunologic reaction suspected?**

Based on the history, physical examination, and objective confirmatory tests, and with an appreciation of hypersensitivity manifestations produced by specific drugs, an immunologically mediated drug reaction is often suspected and can be differentiated from other adverse drug reactions.

Drug hypersensitivity should be strongly suspected when (1) the symptoms and physical findings are compatible with an immune drug reaction; (2) there is (or was) a definite temporal relationship between administration of the drug and an adverse event; (3) the class and structure of the drug have been associated with immune reactions; (4) the patient had previously received the drug on one or more occasions; (5) there is no other clear cause for the presenting manifestations in a patient who is receiving medications known to cause hypersensitivity reactions; and (6) the skin tests and/or laboratory findings are compatible with drug hypersensitivity.

Involvement of the skin is often a prominent physical sign of drug hypersensitivity. The spectrum of drug-induced skin lesions includes urticaria, morbilliform rashes, papulovesicular and bullous eruptions, and exfoliative dermatitis. Acute life-threatening anaphylactic reactions may involve the cardiorespiratory system with corresponding changes in vital signs. Drug hypersensitivity reactions may also present as fever. In addition, allergic reactions to many drugs may present with a wide array of abnormal physical findings involving mucous membranes, lymph nodes, kidneys, liver, pleura, lungs, joints, and other organs/tissues.

Typical examples of drug allergy include (1) urticaria, laryngeal edema, and hypotension immediately following penicillin administration; (2) anemia in a patient receiving large doses

of penicillin; (3) fever, arthralgias, lymphadenopathy, and an urticarial rash 10 to 14 days after an injection of penicillin; and (4) manifestations of contact dermatitis at a site where a topical medication was applied. The patient's presentation may not always be as typical as these examples. For example, patients experiencing an IgE-mediated reaction from penicillin can present with manifestations of an acute cardiac event if sufficient amounts of mediators are released from mast cells in the heart.

**\*ANNOTATION 4: The adverse reaction is due to expected or unexpected non-immune adverse events, idiosyncrasy, intolerance or pseudoallergic effects of the drug**

Most adverse drug reactions are in this category. The spectrum of expected or unexpected non-immune side effects is often specific to the drug or drug class. Clinical presentations of idiosyncratic and intolerance reactions are often characteristic for certain drugs [(eg, quinidine, aspirin/nonsteroidal anti-inflammatory drugs (ASA/NSAIDS)]. Tinnitus occurring after a subtherapeutic dose of quinidine or hemolytic anemia induced by dapsone in patients with glucose-6-phosphate dehydrogenase deficiency are examples of idiosyncrasy. Intolerance to ASA/NSAIDS, as manifested by life-threatening bronchospasm, may develop in patients with asthma and nasal polyps. By contrast, pseudoallergic reactions are often symptomatically identical to IgE-mediated drug allergy, may occur without a prior history of exposure or sensitization and lack a defined immunologic mechanism. The latter category of adverse drug reactions may be corroborated by test dosing or graded challenge tests by experienced allergists.

**\*ANNOTATION 4A: Future management and prevention of non-immune adverse drug reactions**

Dose modification may be possible in specific instances of toxicity, side effects or drug interactions. In most cases, the drug should be discontinued

and if available, a suitable alternative drug should be used. If the drug is essential, gradually increasing doses of the drug may be administered by various graded challenge regimens. Cautious use of some agents that induce severe pseudoallergic reactions (eg, radiocontrast media dyes) may be possible if patients are pre-treated with a combination of glucocorticosteroids and H<sub>1</sub>/H<sub>2</sub> antihistamines. Preventive measures include education of the patient about the potential severity and treatment of subsequent reactions, avoidance of the drug and cross-reactive drugs, and personal use of Medic-Alert tags and/or bracelets.

**\*ANNOTATION 5: Perform appropriate tests (if available) to confirm immunopathogenesis**

Diagnosis of many cases of drug hypersensitivity is presumptive as specific confirmatory tests are usually not available. Useful clinical testing is predicated on the immunopathogenesis of the drug hypersensitivity reaction. The diagnostic potential of percutaneous and intracutaneous tests in IgE-mediated allergy induced by large molecular weight biologicals is comparable to similar test reagents used in the diagnosis of inhalant allergy. However, in most cases adequate data are not available to determine the predictive value of skin testing except to penicillin and insulin. In situations where skin testing cannot be interpreted properly (ie, generalized eczema, dermatographism or lack of response to the positive histamine control) some in vitro assays for specific IgE are available. However, they are not as sensitive as skin tests and generally do not have negative predictive value. A diagnosis of anaphylaxis may be confirmed retrospectively by a rise in serum  $\beta$ -tryptase, which peaks at 1 to 2 hours and remains elevated 2 to 4 hours after the reaction or by an increase in the level of histamine/N-methylhistamine in urine collected for 24 hours after the reaction.

Immunopathogenesis of delayed drug reactions consistent with cytotoxic or immune complex Gell-

Coombs categories may be confirmed by nonspecific and specific laboratory tests. Under these circumstances, tests such as a complete blood count, total eosinophil and platelet counts, sedimentation rate or C-reactive protein, nuclear and/or cytoplasmic autoantibodies, complement components (C3, C4) cryoglobulins, and/or a C1q binding assay may be appropriate. Indirect and direct Coombs tests are often positive in drug-induced hemolytic anemia and specific tests for immunocytotoxic thrombocytopenia and granulocytopenia are available in some medical centers.

Contact dermatitis can usually be verified by drug-specific epicutaneous patch tests. Because sensitized T cells have been demonstrated in a variety of non-IgE, non-contactant cutaneous drug reactions, patch tests may also be a helpful diagnostic adjunct, especially when a patient has received multiple drugs. Lymphocyte proliferation tests and isolation of specific T cell clones can be demonstrated in some of these cases. The predictive value of patch and in vitro tests is unknown and they are not available in most medical centers.

When laboratory tests are not diagnostic or available in non-IgE-mediated drug reactions, cautious provocative drug challenges under controlled conditions may be considered if the risk of using the drug is considered to be less than the underlying disease. Under no circumstances should such drug challenges be conducted in cases of severe, life-threatening immunocytotoxic reactions, vasculitic syndromes, exfoliative dermatitis, erythema multiforme major/Stevens-Johnson syndrome, or toxic epidermal necrolysis.

**\*ANNOTATION 6: Test(s) positive**

A positive immediate hypersensitivity skin test using non-irritant concentrations of drug suggests that the patient has specific IgE antibodies to the drug being tested and is at significant risk for anaphylaxis or less severe immediate hypersensitivity reactions such as urticaria or angioedema. The positive and negative predictive value

of immediate hypersensitivity skin tests varies depending upon the agent being tested. A positive skin test to the major and/or minor determinants of penicillin has a high predictive value of an immediate hypersensitivity reaction to penicillin. If the skin test(s) is positive, there is at least a 50% chance of an immediate reaction to penicillin. Positive skin tests to protein agents (eg, insulin, heterologous antisera, chymopapain, and streptokinase) generally have good positive predictive value, although large scale prospective studies to determine this index have not been conducted for all of them. The positive and negative predictive values of skin testing to antibiotics other than penicillin are not well established. *Nevertheless, positive immediate hypersensitivity skin tests to non-irritant concentrations of non-penicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents. Unfortunately, substantive data are limited on what constitutes a non-irritant concentration.* A positive in vitro test for specific IgE reaction to a drug or biological (eg, the major determinant of penicillin, insulin, chymopapain, protamine) also indicates significant risk for an immediate reaction but such in vitro tests are generally less sensitive for identifying risks than properly performed skin tests.

As discussed in ANNOTATION 5, various nonspecific and drug specific tests may help to confirm which immunopathogenic pathway is involved.

**\*ANNOTATION 7: Diagnosis of drug hypersensitivity/immunologic reactions confirmed**

The diagnosis of drug hypersensitivity is confirmed by appropriate specific or nonspecific skin and laboratory tests as discussed in ANNOTATIONS 5 and 6. Drug-specific tests are most useful for the diagnosis of Gell-Coombs Types 1 and 4 and occasionally Type 2 reactions. Various nonspecific immunologic tests discussed in ANNOTATION 5 may aid in the diagnosis of Type 3 responses and atypical drug reactions with clinical manifesta-

tions suggesting mixed immunopathogenic mechanisms. It should be emphasized that positive skin or in vitro tests for IgE-mediated reactions have no relationship to non-IgE immune-mediated reactions such as immune complex diseases, immunocytotoxic reactions, life-threatening blistering syndromes or vasculitic disorders.

**\*ANNOTATION 7A: Management**

Acute anaphylactic reactions require immediate discontinuation of the drug and prompt emergency measures which consist of (1) oxygen; (2) maintenance of the airway; (3) IM or SC epinephrine [adults, 0.2 to 0.5 mL of a 1:1000 (1 mg/mL, wt/vol) dilution every 10 to 15 minutes up to a maximum dose of 1.0 mL; children, 0.01 mL (0.01 mg)/kg body weight up to a maximum of 0.5 mL per dose of a 1:1000 dilution, repeated every 15 minutes for 2 doses, then every 4 hours as needed]; (4) parenteral diphenhydramine (1 to 2 mg/kg or 25 to 50 mg); (5) intravenous hydrocortisone, primarily for a late response; (6) intravenous fluids and vasopressors for hypotension; and (7) CPR as needed. These are discussed in detail in "The Parameters for Diagnosis and Management of Anaphylaxis" (J Allergy Clin Immunol 1998;101: S482-S484).

If symptoms do not resolve spontaneously in non-IgE-mediated reactions, additional symptomatic therapy may be indicated. In the case of immune complex reactions, antihistamines and non-steroidal anti-inflammatory drugs may be beneficial. In more severe cytotoxic, immune complex or T-cell mediated reactions, glucocorticosteroids may be indicated. *However, the use of glucocorticosteroids in advanced stages of the erythema multiforme major/Stevens-Johnson syndrome and toxic epidermal necrolysis is controversial and may be harmful.*

The drug should be avoided in the future and alternative drugs should be used. If this is not possible, desensitization or graded challenge procedures should be considered, preferably under

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the supervision of an experienced allergist/immunologist to prevent or attenuate a reaction. The prophylactic regimens before graded challenge or desensitization may be necessary in some cases and are the same as those described in ANNOTATION 4A. Future use of a drug(s) causing a non-anaphylactic, life-threatening reaction (eg, Stevens-Johnson, toxic epidermal necrolysis, Churg-Strauss syndrome, and exfoliative dermatitis) is absolutely contraindicated.

Every effort should be made to prevent allergic reactions to medications. Cross-reactivity between chemically-related drugs should be anticipated. Medications should be prescribed only for medically sound indications and polypharmacy should be minimized, if possible. Orally administered drugs are less likely to produce systemic reactions than drugs given topically or parenterally.

Patients should be carefully instructed about avoiding the drug that caused the reaction and possible cross-reactive drugs. Patients also need to be informed about agents that could be present in over-the-counter preparations having trade names that do not identify the drug. Emergency measures for the treatment of anaphylaxis such as prompt use of self-administered epinephrine and antihistamines should be fully explained. In such situations, patients should not hesitate to call 911 or other emergency help telephone numbers. Patients should be encouraged to carry Medic-Alert tags or wear Medic-Alert bracelets as a useful way of alert-

ing their physicians to previous drug reactions, thereby preventing inadvertent readministration of the drug.

**\*ANNOTATION 8: Does test have high negative predictive value?**

If an in vivo or an in vitro test is negative for specific IgE antibodies directed against the drug, the likelihood that the patient will tolerate the drug depends upon the negative predictive value of the test. The negative predictive values for insulin and chymopain are very good. The only small molecular weight drug for which reliable negative predictive testing information exists is penicillin. If skin tests for the major and minor determinants of penicillin are negative, 97% to 99% of patients (depending on the reagents used) will tolerate the drug without risk of an immediate reaction. The negative predictive value of commercial in vitro tests for penicillin hypersensitivity is poor because they are relatively insensitive and do not test for minor determinants. Tests for other small molecular weight drugs have unknown negative predictive values. Therefore, the likelihood of developing an IgE-mediated reaction cannot be ruled out by either skin or in vitro tests for such drugs. Valid negative predictive test values are not available for drugs which induce cytotoxic or immune complex reactions. The negative predictive value of tests for some common topical sensitizers is generally good (eg, local anesthetics).

**\*ANNOTATION 9: Patient not allergic to this drug**

Within the limitations discussed in ANNOTATIONS 7 and 8, negative tests for IgE-mediated, cytotoxic, immune complex, or contactant hypersensitivity may indicate that the patient is not allergic to the suspected drug and the drug may be administered.

**\*ANNOTATION 10: Patient possibly allergic with negative drug-specific or nonspecific tests**

The suspicion of drug hypersensitivity cannot be confirmed by drug-specific tests in many cases. For the vast majority of drugs causing hypersensitivity reactions, valid confirmatory test materials are not available. Further, comparable data about the allergenicity of the parent compound and its reactive end products or metabolites have only been determined for penicillin drugs. Since the general availability of tests for cytotoxic drug reactions is limited, a conclusion about the allergic basis of such reactions can only be interpreted from the history, physical examination, and nonspecific tests. Similarly, only nonspecific laboratory tests can be utilized for the evaluation of drug-mediated immune complex disease. There are a number of drug reactions for which immunologic mechanisms are strongly suspected but cannot be proved. Thus, the diagnosis of the vast majority of allergic drug reactions is presumptive, based on the characteristic features of history, physical examination, and nonspecific laboratory adjunctive tests without definitive confirmation by positive drug-specific tests.

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# Part 2: Summary Statements Evidence-Based Commentary

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## I. INTRODUCTION

- Adverse drug reactions are a major health problem in the United States.
- About 25% of all adverse drug reactions are due to idiosyncratic/intolerant/allergic/pseudoallergic mechanisms.
- The majority of serious adverse drug reactions are not detected prior to approval of a drug by the United States Food and Drug Administration.

## II. DEFINITIONS

- Drug idiosyncrasy and drug intolerance are non-immune-mediated adverse drug effects (see glossary).
- Drug hypersensitivity is an immunologically mediated response to pharmaceutical and/or formulation (excipient) agents in a sensitized patient.
- Pseudoallergic or anaphylactoid reactions are non-immune responses caused by release of mediators from mast cells and basophils.

## III. CLASSIFICATION OF IMMUNOLOGICALLY MEDIATED DRUG HYPERSENSITIVITY REACTIONS

- Drug allergy may be partly classified by the Gell and Coombs classification paradigm of human hypersensitivity (Type 1: IgE-mediated; Type 2: cytotoxic; Type 3: immune complex; and Type 4: cellular immune-mediated). Some reactions manifest mixed immune mechanisms; others cannot as yet be classified by this method.
- Drug allergy may also be characterized by the predominant tissue/organ involvement (systemic, cutaneous, and/or visceral).

- To some extent, the structural characteristics of drugs and biologic products predict the type of hypersensitivity reaction.

## IV. RISK FACTORS

- The most important risk factors for drug hypersensitivity are related to chemical properties and molecular weights of drugs.
- Other drug-specific risk factors include the dose, route of administration, duration of treatment, repetitive exposure to the drug, and concurrent illnesses.
- Host risk factors include age, gender, atopy, and specific genetic polymorphisms. Many drug reactions occur independent of these risk factors.

## V. CLINICAL EVALUATION AND DIAGNOSIS OF DRUG HYPERSENSITIVITY

- The history should focus on previous and current drug use, the toxicity/allergenicity of previously or currently used drugs and the temporal sequence of events between initiation of therapy and onset of symptoms.
- Physical examination should include all systems that could possibly account for the clinical presentation.
- Possible clinical tests might include but are not limited to a chest x-ray, EKG, a complete blood count with differential, sedimentation rate or C-reactive protein, autoantibody tests, and specific immunologic tests.
- The most useful test for detecting IgE-mediated drug reactions caused by penicillin and many large molecular weight biologicals is the immediate hypersensitivity skin test.
- Specialized immunologic tests are sometimes able to confirm the

immunologic basis of drug-induced cytotoxic reactions.

- Patch testing is the most reliable technique for diagnosis of contact dermatitis. Although it may also prove to be a helpful adjunct in the diagnosis of other non-IgE cutaneous reactions, it has not been standardized for this purpose.
- Lymphocyte proliferation assays may have utility as retrospective indicators of a cell-mediated drug reaction but their positive and negative predictive values have not been determined and they are not available in most medical centers.

## VI. MANAGEMENT AND PREVENTION OF DRUG HYPERSENSITIVITY REACTIONS

- Anaphylactic drug reactions require prompt emergency treatment as discussed extensively in “Practice Parameters for the Diagnosis and Treatment of Anaphylaxis” (J Allergy Clin Immunol 1998;101:S512–S515).
- For mild drug reactions, simple withdrawal of the drug may be all that is required.
- Glucocorticosteroids may be required for severe and/or progressive immune complex and cytotoxic-mediated drug reactions and early stages of suspected erythema multiforme major/Stevens-Johnson syndrome.
- Desensitization may be required if there is no possible alternative for a drug that has caused anaphylaxis.
- Slower graded challenge regimens may be utilized to allow patients to tolerate drugs associated with a variety of non-IgE mediated hypersensitivity reactions.



- Prevention of allergic reactions may be accomplished by attention to the following principles: (1) a careful history to determine host risk factors; (2) avoidance of cross-reactive drugs; (3) use of predictive skin tests when available; (4) proper and prudent prescribing of drugs (especially antibiotics) frequently associated with adverse reactions; and (5) use of oral in preference to parenteral drugs when possible.

## VII. PROTOTYPES OF IMMUNOLOGICALLY MEDIATED DRUG HYPERSENSITIVITY

### A. IgE-mediated reactions (Gell-Coombs Type 1)

#### 1. Beta lactam antibiotics

- Although penicillin hypersensitivity may encompass Types 1 to 4 of the Gell-Coombs classification, the most dreaded complication is anaphylaxis.
- Penicillin is a frequent cause of anaphylaxis and has been estimated to be responsible for the majority of all drug-mediated anaphylactic deaths in the United States.
- Although IgE-mediated reactions may occur after administration of penicillin by any route, parenteral administration is more likely to cause anaphylaxis. Oral administration may be safer.
- Patients with a history of a prior penicillin reaction are six times more likely to experience a reaction on subsequent exposure compared with those without a previous history.
- Patients with a positive family history but a negative personal history of penicillin allergy do not require penicillin skin testing because they are not at greater risk of having an allergic reaction to penicillin than the general population.
- Penicillin-specific IgE diminishes over time. Approximately 70% of adults with documented penicillin allergy have no detectable IgE when tested 10 years later.
- If a patient requires penicillin and has a past history of penicillin allergy, it is necessary to skin test the patient for the presence of penicillin-specific IgE antibodies in order to determine the risk of an immediate hypersensitivity reaction.
- Skin tests should be performed with the major (penicilloyl polylysine) and minor determinants of penicillin. The major determinant reagent, PrePen® may be obtained commercially, but minor determinant mixtures are only available in certain medical centers. Because minor determinant mixtures are not commercially available, penicillin G is an acceptable substitute, recognizing that there is a slight risk of a false negative skin test because it does not contain all relevant antigenic determinants. Skin tests to both major and minor determinants of penicillin are necessary because about 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant.
- Evaluation by *in vitro* tests (eg, ELISA or RAST) does not reliably rule out the presence of specific IgE antibodies to penicillin because of the relative insensitivity of these tests and they are only available for the major (penicilloyl) determinant.
- If a patient has a positive history and positive skin tests to the major and/or minor determinants of penicillin, there is at least a 50% chance of an immediate hypersensitivity reaction if penicillin is given again.
- If skin tests to the major (penicilloyl) and minor determinants (minor determinant mixture or penicillin G) of penicillin are negative, 97% to 99% of patients (depending on the reagents used) will not develop an immediate hypersensitivity reaction after administration of penicillin. When skin tests with the above reagents are employed by skilled personnel using proper technique, serious reactions, including anaphylaxis and death, are extremely rare.
- Skin testing for penicillin-specific IgE does not predict reactions occurring more than 24 hours after administration of drug. These include later onset cutaneous rashes, non-IgE-mediated immune complex syndromes and bullous, mucocutaneous responses.
- If a patient has a past history of an immediate reaction to penicillin and the skin test is positive to either major or minor determinants, the patient should receive an alternative antibiotic unless there is no acceptable alternative to penicillin. If administration of penicillin is mandatory in this setting, desensitization is necessary.
- Administration of ampicillin and amoxicillin is associated with the development of morbilliform rashes in 5% to 13% of patients. These patients are not considered to be at risk of a life-threatening reaction to penicillin and therefore do not require skin testing before penicillin administration. On the other hand, if the rash to ampicillin or amoxicillin is urticarial, the patient should undergo penicillin skin testing before a future course of penicillin is given. When the history is unclear, skin testing should be done.
- Carbapenems (eg, imipenem) are cross-reactive with penicillin. Aztreonam, a monobactam, rarely cross-reacts with penicillin.
- Cephalosporins and penicillins have a common  $\beta$ -lactam ring structure, and varying degrees of *in vitro* cross-reactivity have been documented. Although the risk of allergic reactions to cephalosporins in patients with positive skin tests to penicillin appears to be low (less than 2%), first generation cephalosporins may pose a greater risk than second or third generation cephalosporins.

- If a patient has a history of penicillin allergy and requires a cephalosporin, skin testing to major and minor determinants (ie, penicillin G or a minor determinant mixture, if available) of penicillin preferably should be done to determine if the patient has penicillin-specific IgE antibodies. If skin tests are negative, the patient can receive a cephalosporin at no greater risk than the general population.
- If the skin tests are positive to penicillin, the physician's recommendations may include: (1) administration of an appropriate alternative antibiotic; (2) a cautious graded challenge (test dosing) with appropriate monitoring, recognizing that there may be a 2% chance of inducing an anaphylactic reaction; or (3) desensitization to the cephalosporin that is proposed for use. A recent survey of anaphylactic deaths due to cephalosporins administered to patients with documented penicillin/amoxicillin sensitivity indicates that catastrophic outcomes have occurred when these precautions are ignored.
- Patients who require penicillin and have a history of an IgE-mediated reaction to a cephalosporin should undergo penicillin skin testing. If the test is negative, they can receive penicillin; if positive, they should either receive an alternative medication or undergo desensitization to penicillin.
- If a patient with a past history of allergy to one cephalosporin requires another cephalosporin, skin testing with the required cephalosporin can be done, recognizing that the negative predictive value is unknown. If the skin test response to the cephalosporins is positive, the significance of the test should be checked further in control subjects to determine if the positive response is IgE-mediated or caused by irrita-

tion (ie, use of a concentration that is directly irritant).

## 2. Non-beta lactam antibiotics

- The overall incidence of hypersensitivity to these agents is 1% to 3%.
  - Trimethoprim-sulfamethoxazole induces many of these reactions, particularly in patients with AIDS.
  - If the history is consistent with an allergic reaction to a specific agent, the best decision is to switch to an acceptable alternative drug.
  - If a non-beta lactam drug is needed urgently, desensitization or cautious graded challenge may be required, depending on the history.
  - Skin test protocols are available for some non beta-lactam antibiotics but their positive and negative predictive values are unknown because they have not been standardized and relevant drug metabolites are unknown.
  - IgE mediated anaphylaxis may occur after administration of any non-beta lactam antibiotic.
  - The "red man's syndrome" due to nonspecific histamine release is commonly observed after administration of vancomycin. It can be prevented by slowing the rate of intravenous infusion and/or preadministration of H<sub>1</sub> blockers.
- ## B. Cytotoxic reactions (Gell-Coombs Type 2)
- Immunocytotoxic reactions are serious and potentially life-threatening.
  - Immuno-hemolytic anemias have occurred after treatment with quinidine,  $\alpha$ -methyl dopa and penicillin.
  - In the case of penicillin, these reactions occur in patients receiving very large doses of the drug.
  - Specific penicillin IgG antibodies have been identified in such reactions.
  - Positive direct and indirect Coombs' tests in immunohemolytic anemia may reflect the presence of penicillin-specific IgG,

complement or an autoantibody to an Rh determinant on the red cell membrane.

- Immune-induced thrombocytopenia has been observed in the course of treatment with quinidine, sulfonamides and other drugs. Platelet membrane damage is mediated by interaction of drug and immune complexes adsorbed onto platelet membranes.
- Immune-mediated granulocytopenia is uncommon but may be induced by a variety of drugs.

## C. Immune complex reactions (Gell-Coombs Type 3)

- These occur after use of heterologous antisera, murine monoclonal antibodies and some small molecular weight drugs, such as penicillin.
- Symptoms and signs typically may occur from 1 to 3 weeks after the last dose of drug.
- The immunopathogenesis of immune complex disease involves IgG and/or IgM immune complexes and in some cases, coincidental IgE antibodies.
- Treatment consists of H<sub>1</sub> blockers for control of cutaneous symptoms and in severe cases, high doses of glucocorticosteroids.

## D. Cell-mediated reactions (Gell-Coombs Type 4)

- Contact dermatitis produced by topical drugs and/or excipients contained in the topical formulation is the most common type of cell-mediated reaction.
- Patch testing at proper concentrations is often successful in detection of suspected or unsuspected contactant allergens.
- After avoidance is instituted, topical and/or systemic glucocorticosteroids may be required for total clearing of the dermatitis.

## E. Miscellaneous Syndromes

- Many drugs, hematopoietic growth factors, cytokines and interferons are associated with vasculitis of skin and visceral organs.
- Some drugs (eg, hydralazine and procainamide) may induce a lupus-like syndrome.

- Some anticonvulsant drugs (eg, phenytoin, carbamazepine) may cause a life-threatening systemic hypersensitivity syndrome, originally termed pseudolymphoma, with diffuse inflammation of the liver and kidney.
  - Pulmonary manifestations of allergic drug reactions include lupus-like reactions, alveolar or interstitial pneumonitis, non-cardiogenic pulmonary edema, granulomatosis and fibrosis.
  - The Churg-Strauss syndrome, a systemic granulomatous vasculitis, has been reported in an increasing number of patients receiving glucocorticosteroids alone, leukotriene receptor antagonists for asthma with or without glucocorticosteroids and macrolide antibiotics. A causal relationship between these drugs and the Churg-Strauss syndrome has not been established.
  - Immunologic hepatitis may occur after sensitization to para-aminosalicylic acid, sulfonamides, and phenothiazines.
  - Immunologic nephropathy may present as interstitial nephritis (a classical example is methicillin) or as a membranous glomerulonephritis (eg, gold salts, penicillamine).
  - Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions including erythema multiforme/minor, erythema multiforme major/Stevens-Johnson syndrome and toxic epidermal necrolysis. The suspected drug should be discontinued promptly if any of these conditions is suspected.
  - *The effectiveness of glucocorticosteroids in the treatment of the erythema multiforme major/Stevens-Johnson syndrome is controversial but if used, they should be started as early in the course of the disease as possible.*
  - Toxic epidermal necrolysis should be treated in a burn unit. Glucocorticosteroids are contraindicated because they cannot affect toxic epidermal necrosis and they add a significant risk of infection in these patients.
  - Cancer chemotherapeutic agents such as L-asparaginase, doxorubicin, cisplatin, and carboplatin may be associated with IgE-mediated anaphylaxis. Cremophor-EL, a lipid solvent vehicle for paclitaxel, and several other chemotherapeutic agents may cause anaphylactoid reactions.
  - Reactions due to blood and blood products include urticaria and rarely, anaphylaxis in patients with complete IgA deficiency.
  - Immediate generalized reactions may occur in patients receiving protamine for reversal of heparinization after cardiopulmonary bypass and hemodialysis. Diabetic patients receiving protamine-containing insulin are at significantly greater risk for developing these reactions.
  - Adverse reactions to heparin include localized urticarial rashes, anaphylaxis, and thrombocytopenia. The latter may be associated with sudden massive thrombosis and necrosis.
  - Many agents have been reported to cause anaphylactic/anaphylactoid reactions during the operative and perioperative periods. Diagnosis and management of these reactions are discussed in greater detail in the "Practice Parameters for Diagnosis and Treatment of Anaphylaxis" (J Allergy Clin Immunol 1998;101:S512-S515).
  - Most adverse reactions to local anesthetics are due to nonallergic factors that include vasovagal responses. To exclude the extremely rare possibility of an immune mediated-reaction, a simple graded challenge should be performed in a patient who presents with a history of a possible allergic reaction.
- VIII. PSEUDOALLERGIC REACTIONS**
- Although pseudoallergic manifestations can mimic IgE-mediated allergic reactions, prior sensitization and specific IgE antibodies cannot be demonstrated in patients who have had such reactions. A variety of drugs and excipients may cause such reactions.
  - Opiates and their analogs may induce pseudoallergic reactions in many patients.
  - Anaphylactoid reactions to radiocontrast media (RCM) can occur after intravascular administration and during hysterosalpingograms, myelograms, and retrograde pyelograms.
  - Anaphylactoid reactions to RCM are clinically indistinguishable from IgE-mediated immediate hypersensitivity anaphylactic reactions, although they do not appear to be associated with drug-specific IgE antibodies or other types of immunologic reactions.
  - The treatment of anaphylactoid reactions to RCM is not different than the treatment of anaphylactic reactions caused by allergen-specific IgE interactions and resultant mast cell/basophil mediator release.
  - Patients who have experienced previous anaphylactoid reactions during the administration of RCM are at risk for a repeat reaction. Estimates of this risk range from 16% to 44% for procedures with high osmolality RCM. The physician should therefore consider other diagnostic alternatives for such patients rather than procedures that require readministration of RCM.
  - If such a procedure is necessary, pretreatment and the use of lower osmolar RCM will reduce the risk of repeat anaphylactoid reactions to approximately 1%.
  - Pretreatment regimens for prevention of repeat anaphylactoid reactions consist of oral glucocorticosteroids, H<sub>1</sub> and H<sub>2</sub> antihistamines, *and possibly other medications such as ephedrine or albuterol.*
  - Anaphylactoid reactions may occur after treatment with colloid

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volume expanders, mannitol, Cre-mophor El, preservatives, ASA, NSAIDs, and several antibiotics.

### **IX. NON-IMMUNE DRUG IDIOSYNCRASY/INTOLERANCE REACTIONS**

- ASA and NSAIDs are associated with a variety of non-IgE-mediated adverse effects. These include rhinoconjunctivitis, bronchospasm, urticaria, angioedema, and laryngeal edema.
- There is no definitive skin or in vitro test to identify patients who may react to ASA or other NSAIDs. On the other hand, carefully performed oral ASA/NSAID challenges may be useful in confirming the diagnosis.
- If an oral challenge to ASA/NSAIDs is indicated, referral to an allergist-immunologist and/or a well-equipped and experienced medical facility is appropriate because of the possibility of life-threatening reactions that can occur during such challenges.
- Once a diagnosis of ASA/NSAIDs intolerance has been made, avoidance is essential for prevention of life-threatening reactions to these agents. This requires educating the patient about combination products (including over-the-counter medications) containing ASA or NSAIDs.
- If the ASA/NSAID challenge is positive, pharmacologic desensitization and subsequent continued treatment with ASA or NSAIDs may be justified if there is a sound medical indication for this strategy.
- Angiotensin-converting enzyme (ACE) inhibitors are associated

with two major adverse effects: cough and angioedema.

- ACE-induced cough may occur in 10% to 25% of patients. The cough disappears within several weeks after discontinuation of the drug.
- Angioedema is a potentially life-threatening complication of ACE inhibitors. About 1/3 of patients experiencing these reactions require hospitalization and 10% require intensive care including intubation.
- Non-immune-mediated cough and bronchoconstriction may occur in susceptible asthmatic patients exposed to benzalkonium chloride and sulfites.

### **X. ADVERSE DRUG REACTIONS IN PATIENTS WITH HIV INFECTION/AIDS**

- Drug reactions are common in patients with AIDS and, in some cases the incidence of reactions may be related to the degree of immunodeficiency.
- Adverse reactions to sulfonamides and trimethoprim-sulfamethoxazole (TMP-SMX) may complicate both treatment and prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in patients with AIDS.
- The most common type of reaction to sulfonamides is a morbilliform, maculopapular eruption often associated with fever that occurs after 7 to 12 days of therapy. Immediate reactions (anaphylaxis, urticaria, and mucosal angioedema) and other delayed reactions (erythema multiforme minor, erythema multiforme major/Stevens Johnson syndrome, toxic epider-

mal necrolysis, hepatic, hematological and renal manifestations, and immune complex reactions) may also occur.

- TMP-SMX-specific IgG and IgM antibodies have been found in AIDS patients either with or without skin reactions to SMX. It is not known whether these antibodies play a pathogenic role in SMX hypersensitivity reactions.
- For those individuals who develop maculopapular rashes after TMP-SMX administration, several desensitization or graded challenge protocols have been developed and used successfully. Empirically, reintroduction of a sulfonamide by one of these protocols is generally done several weeks after the initial adverse reaction but it may be started earlier if treatment of a serious infection requiring these drugs is necessary.
- These regimens should not be used in individuals with a history of erythema multiforme major/Stevens-Johnson syndrome or toxic epidermal necrolysis.
- Sulfadiazine, acyclovir and zidovudine graded challenge protocols have been utilized for patients with AIDS.
- In addition to sulfonamides, patients with AIDS may have an increased frequency of adverse reactions to a number of other agents including anti-mycobacterial agents, pentamidine, amoxicillin-clavulanic acid, clindamycin, primaquine, carbamazepine, phenytoin, thalidomide, foscarnet, and zidovudine.

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# Evidence-Based Commentary

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## I. INTRODUCTION

Adverse drug reactions cause major health problems in the United States. There are about 106,000 fatalities due to adverse drug reactions in the United States per year.<sup>1</sup> The overall incidence of serious adverse drug reactions of hospital patients is 6.7% (95% CI, 5.2% to 8.2%). Approximately 25% of both serious and non-serious adverse drug reactions are caused by idiosyncrasy/intolerance, pseudoallergic and/or allergic adverse drug reactions. Drug idiosyncratic and/or intolerant reactions, as defined in the glossary, are non-immune, unpredictable occurrences. Such reactions occur in only a small percentage of patients and precise mechanisms have not been established. Adverse drug reactions constitute either the fourth or the sixth leading cause of death in the United States depending on whether one uses the lower (76,000 patients) or the upper (137,000 patients) confidence limit.

Physicians should become fully acquainted with the proper ways of recognizing and preventing such reactions. Further, since 51% of all approved drugs have serious adverse effects not detected prior to approval by the FDA, there have been an increasing number of appeals for more comprehensive monitoring of marketed drugs.<sup>2,3</sup>

## II. DEFINITIONS

Drug allergy/hypersensitivity reactions are immunologically mediated responses to pharmacologic agents and pharmaceutical excipients. Such reactions may occur after exposure to a wide variety of chemicals (oral, parenteral, or topical), biologics (derived from natural or recombinant technology sources) and "inert substances" (excipients) used in the formulation of active drug products.

These reactions must be distinguished from pseudoallergic or anaphylactoid reactions induced by substances such as radiocontrast media, colloid volume ex-

panders, basic polypeptides, opiates, ASA/NSAIDs and "inert" excipients. Pseudoallergic or anaphylactoid reactions are caused by direct release of mediators from mast cells and basophils, resulting in the classic end-organ effects that these mediators exert.<sup>4</sup> Direct mediator release occurs without evidence of a prior sensitization period, specific IgE antibodies or antigen-antibody bridging on mast cells/basophil cell membranes. This non-immune reaction is immediate, often severe and therefore referred to as anaphylactoid. Because it is not immunologic, it may occur the first time that the host is exposed to a particular agent. Some drugs induce both allergic and pseudoallergic reactions. An example of this type of drug is vancomycin which may elicit the pseudoallergic "red man syndrome" as well as true IgE-mediated anaphylaxis. Anaphylactoid reactions have also been reported after the first treatment with quinolones.

Drug idiosyncrasy/intolerance responses may mimic immunologically mediated drug reactions. Three major classes of drugs have been shown to induce such reactions: aspirin (ASA), non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, as well as several preservatives. As cited above, some immediate cardiorespiratory reactions to ASAs and NSAIDs occur within minutes and strongly resemble anaphylactoid reactions.

## III. CLASSIFICATION OF IMMUNOLOGICALLY MEDIATED DRUG HYPERSENSITIVITY REACTIONS

Clinical presentations of drug allergy are often diverse, depending on type(s) of immune responses and target organ specificity(ies). If immunopathogenesis is mixed, some drug reactions may be difficult to classify by criteria previously established for naturally occurring human hypersensitivity. On the

other hand, the characteristics and mechanisms of many allergic drug reactions are consistent with the chief categories of human hypersensitivity defined by the Gell-Coombs classification of human hypersensitivity [immediate hypersensitivity (Type 1), cytotoxic (Type 2), immune complex (Type 3), and cell mediated (Type 4)].<sup>5</sup>

Immediate hypersensitivity Type 1 reactions are IgE mediated and result in immediate reactions such as anaphylaxis. These are exemplified by symptoms of urticaria, laryngeal edema, wheezing, and cardiorespiratory collapse. Common causes are large molecular mass biologicals and many drugs (eg, penicillin). Cytotoxic reactions are induced by complement-mediated cytotoxic IgM or IgG antibodies which are formed in response to drug altered cell surface membranes. Classic examples of this phenomenon are acquired hemolytic anemia induced by  $\alpha$  methyl dopa and penicillin or thrombocytopenia caused by quinidine. Type 3 reactions are mediated by immune complexes formed in slight antigen excess. The chief manifestations of these reactions include fever, rash, urticaria, lymphadenopathy and arthralgias, which typically appear 1 to 3 weeks after the last dose of an offending drug and subside when the drug and/or its metabolites are completely eliminated from the body. Drugs that are likely to cause these reactions include penicillin, sulfonamides, thiouracil, and phenytoin. Delayed hypersensitivity Type 4 reactions are mediated by cellular immune mechanisms which include CD4+ cells, CD8+ cells, or both. Reactions in this category include contact dermatitis, a condition in which the topical induction and elicitation of sensitization by a drug is entirely limited to the skin. Delayed hypersensitivity responses may also be systemic, involving lymphoid organs and other tissues throughout the body. Sensitized T-cells produce a wide array of pro-

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inflammatory cytokines that ultimately lead to lymphocytic infiltrates, disseminated granulomata, and fibrosis. It has been suggested that there is a marked clinicopathologic similarity between some late onset drug reactions and graft versus host reactions which are initiated and maintained by T cells.<sup>6</sup>

In addition to the Gell and Coombs human hypersensitivity classification, there are a number of drug reactions associated with specific T cell activation, for which immunopathogenesis has not been fully established. These include maculopapular rashes, erythroderma, eczematous rashes, exfoliative dermatitis, drug fever, and fixed drug reactions. The latter are caused by such drugs as barbiturates and sulfonamides. The term "fixed" is applied to this lesion because reexposure to the drug usually produces recurrence of the lesion at the original site. The presence of CD8<sup>+</sup> T lymphocytes has been demonstrated in the peripheral blood and involved skin of patients with drug-induced delayed cutaneous hypersensitivity reactions characterized by morbilliform and bullous exanthematous lesions.<sup>7</sup> Allergen-specific T cell clones from some of these patients displayed a TH 1-like cytokine pattern, as contrasted to CD4<sup>+</sup> positive T cell clones from patients with penicillin-induced urticarial exanthemata, which demonstrated a TH2-like cytokine pattern.<sup>7</sup>

From the clinical standpoint, the most practical method of classifying drug reactions is by predilection for various tissue and organ systems. Cutaneous drug reactivity represents the most common form of restricted tissue responsiveness to drugs.<sup>8</sup> The pulmonary system is also recognized as a favorite site for certain drug hypersensitivity reactions. Other individual tissue responses to drugs include cytotoxic effects upon blood components and hypersensitivity sequelae in liver, kidneys, and blood vessels. Some drugs, however, induce heterogeneous immune responses and tissue manifestations. Thus, sensitization to penicillin or its degradation products may eventuate in anaphylaxis, morbilliform

rashes, serum sickness, drug fever, cytotoxic effects (eg, hemolytic anemia), hypersensitivity vasculitis, interstitial nephritis, or severe contact dermatitis if applied topically. Finally, the temporal relationship to onset of symptoms after administration of a specific drug may constitute another type of classification, ranging from immediate (minutes to an hour), accelerated (1 to 3 days) or delayed beyond 3 days.<sup>9</sup>

To some extent, the structural characteristics of drugs and biological products permit predictions about what type of hypersensitivity reactions to expect from certain classes of therapeutic substances.<sup>6</sup> Allergic reactions to peptides and proteins are most often mediated by either IgE antibodies or immune complex responses. Such reactions may also be mixed. In specific situations, the process may culminate in a multisystem, vasculitic disease of small and medium sized blood vessels. Although immune responses induced by carbohydrate agents are infrequent, anaphylaxis has been described after topical exposure to carboxymethylcellulose.<sup>10</sup> Contact dermatitis is the typical immune response observed after topical exposure to a number of fatty vehicles and essential oils in therapeutic products (lanolin, clove oil, camphor oil, and beeswax).<sup>11-13</sup> Any single or mixed variety of immune responses may occur after exposure to low molecular mass ( $\leq 1,000$  daltons) inorganic or organic medicinal chemicals. The immunogenic potential of such drugs is often determined by one or more reactive end products or metabolites which haptenate with various body proteins. Often, the parent compound itself is not immunogenic because it lacks the ability to conjugate with proteins in a stable covalent linkage. Metabolism of drugs by cytochrome oxidase pathways may occur in the liver, skin, and phagocytic cells. In addition, patients with certain genetic polymorphisms are at higher risk for allergic and autoimmune disorders induced by drugs. Thus the risks of procainamide-induced lupus erythematosus and severe mucocutaneous diseases after sulfonamide treatment are

higher in patients having the slow-acetylator phenotype.<sup>6,14</sup> As a general rule, increases in molecular mass and structural complexity are often associated with increased immunogenicity, at least as far as humoral mediated hypersensitivity is concerned. On the other hand, some proteins (eg, latex) also may induce contact urticaria and/or contact dermatitis in addition to anaphylaxis.

#### IV. RISK FACTORS

The chemical properties, amount/duration of exposure to the drug and host factors may all interact in the development of drug allergy. Large molecular mass agents such as proteins and some polysaccharides may be immunogenic and therefore are much more likely to induce antibody-mediated drug hypersensitivity reactions, especially in atopic individuals. On the other hand, specific structural moieties in non-protein medicinal chemicals are often critical determinants in inducing drug hypersensitivity. How these particular structures (eg, beta lactam rings of penicillins and cephalosporins) are degraded is of crucial importance. Prolonged drug and metabolite(s) clearance may occur because of genetic polymorphisms of metabolic enzyme pathways (eg, hydralazine, azathioprine).<sup>15,16</sup> Specific chemical structure is responsible for cross-sensitivity which may be based either on common core elements (eg, beta lactam rings) or side chains. In some cases, side chain specificity alone may determine drug hypersensitivity.<sup>17-19</sup>

Parenteral and topical administrations of a drug enhance the possibility of sensitization while the oral route of administration may be safer.<sup>20</sup> Topical application of a medicinal chemical may induce contact dermatitis. Single doses of a prophylactic antibiotic are much less likely to sensitize compared with high dose prolonged parenteral administration of the same drug. In the case of penicillin, the latter type of exposure may cause an immune-mediated hemolytic anemia or interstitial nephritis.<sup>9,21</sup> Frequent repetitive courses of therapy are also more likely to sensitize.

Host factors and concurrent medical illnesses are significant risk factors. Drug reactions appear to occur less frequently in infants and in the elderly. Immaturity of the immunologic apparatus is given as an explanation for the former, and involution of the immunologic apparatus may account for the latter.<sup>22</sup> In the prospective study by Bigby et al women were shown to have a 35% higher incidence of adverse cutaneous reactions to drugs than men.<sup>23</sup> In one study, the odds ratio for women developing reactions to RCM was 20-fold greater than for men.<sup>24</sup> Allergic reactions to multiple, structurally unrelated antibiotics tend to occur more often in women.<sup>25</sup> *One recent survey of possible familial drug allergy reported that children of parents who are allergic to at least one antibiotic may have a 15-fold greater risk for subsequent reactions to antibiotics than children without such histories.*<sup>26</sup> A genetic relationship to histocompatibility antigenic determinants (HLA-DR3) exists in patients with rheumatoid arthritis who are treated with gold or penicillamine and subsequently develop drug-induced nephropathy.<sup>27</sup> Patients with systemic lupus erythematosus appear to have an increased prevalence of drug reactions although it is not clear that this predilection is causally related to the underlying immunologic abnormalities or the fact that such patients are exposed more often to drugs. The presence of an atopic diathesis (allergic rhinitis, allergic asthma, and/or atopic dermatitis) predisposes to a higher rate of allergic reactions to proteins (eg, chymopapain) but not to low molecular agents.<sup>28-30</sup> Paradoxically, atopic patients appear to have a greater risk of non-IgE-mediated, pseudoallergic reactions induced by RCM.<sup>31</sup> Atopy appears to be associated with a substantially increased risk of serious allergic reactions (including anaphylaxis) once an IgE antibody response to any drug has developed.<sup>20,32</sup> Therefore, an atopic background increases the risk that an immediate hypersensitivity reaction may be severe, but it does not increase the probability that an IgE-mediated antibody response will de-

velop in response to small molecular mass drugs.

## V. CLINICAL EVALUATION AND DIAGNOSIS OF DRUG HYPERSENSITIVITY

The first question facing the physician in the evaluation of a patient with a suspected adverse drug reaction is whether the clinical problem is drug-related. The subsequent clinical evaluation and diagnosis of drug hypersensitivity reactions is based upon a number of clinical criteria:

- (1) The symptoms and physical findings are compatible with an immune drug reaction;
- (2) There is (or was) a definite temporal relationship between administration of the drug and an adverse event;
- (3) The class and chemical structure of the drug have been associated with immune reactions;
- (4) The patient previously received the drug on one or more occasions (with the possible exception of accelerated serum-sickness-like reactions);
- (5) There is no other clear cause for the presenting manifestations in a patient who is receiving medications known to cause hypersensitivity reactions; and
- (6) Skin tests and/or laboratory findings (if available) are compatible with drug hypersensitivity.

Currently, for most drugs, these questions are answered on the basis of information derived solely from a clinically derived data base.

### A. History

A careful history of previous and current drug usage, focusing particularly on the temporal sequence of events between initiation of therapy and onset of symptoms is probably the most useful factor in the diagnosis of an allergic drug reaction. In this regard, specific knowledge about the toxicology and allergenicity of the involved drugs often is valuable in trying to delineate the causal factor. This is particularly important when a patient is receiving multiple drugs. As previously dis-

cussed, general and specific host risk factors should also be noted in the medical history.

### B. Physical Examination

Since drug reactions may involve virtually any organ system, a careful physical examination is recommended. Cutaneous lesions should be described accurately with regard to gross appearance and distribution. A distinction between maculopapular skin eruptions and urticaria is very important since the latter is more likely to be mediated by specific IgE antibodies. The presence of purpura and petechiae are often cutaneous stigmata of vasculitis.<sup>33</sup> Unusual maculopapular lesions of the sides of the fingers and toes or a serpiginous distribution of such lesions along lateral aspects of both soles may suggest serum sickness.<sup>34</sup> Erythema multiforme minor is a polymorphous maculopapular lesion that spreads peripherally and clears centrally to form an annular pattern known as a "target" lesion. This consists of three zones: an erythematous central papule that may blister, an edematous middle ring, and an erythematous outer ring. *In an exaggerated form, these lesions may develop blisters and progressively involve mucous membranes.*<sup>35</sup> *Although this symptom complex is termed erythema multiforme major and is often used synonymously with the Stevens-Johnson syndrome, some clinicians specify that the two conditions have distinguishing features. Target lesions, particularly on the extremities, are still present in erythema multiforme major while widespread blistering purpuric macules of the face, trunk, and proximal extremities are characteristic of the Stevens-Johnson syndrome.*<sup>33</sup> At this stage, more than one mucosal site is involved and there are progressive constitutional symptoms. The clinical presentation of Stevens-Johnson syndrome may evolve into toxic epidermal necrolysis, a severe drug-induced skin disease in which apoptotic, epidermal cell death results in the separation of large areas of skin at the dermo-epidermal junction, producing the appearance of scalded skin.<sup>33</sup> Fixed drug

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eruptions are pleomorphic, ranging from sharply defined erythematous papules or pigmented areas to edematous, bullous, papulovesicular, or urticarial lesions. Contact dermatitis is a papulovesicular, scaly lesion which appears at cutaneous sites previously exposed to topical medications. Photoallergic dermatitis often has a similar appearance to contact dermatitis. Exfoliative dermatitis is a severe, end stage dermatosis that usually progresses from other types of late onset cutaneous drug reactions and consists of large confluent areas of shedding scaly epidermis. The entire skin is scaly and erythematous; chills and fever are common. Erythema nodosum lesions of the extensor surfaces of the extremities may also be associated with cell-mediated responses induced by drugs.

Acute life-threatening drug reactions can involve the upper and lower respiratory tracts and the cardiovascular system. Vital signs are profoundly affected in the course of anaphylaxis and in some cases expiratory wheezing may be heard (for more detailed discussion of signs and symptoms of anaphylaxis, see "Practice Parameters on Diagnosis and Treatment of Anaphylaxis" *J Allergy Clin Immunol* 1998; 101:S482). Drug reactions may present as an isolated fever, occasionally in excess of 104°F.<sup>36</sup> They may cause a wide array of physical abnormalities including mucous membrane lesions, lymphadenopathy, hepatosplenomegaly, pleuropneumopathic abnormalities, and joint tenderness/swelling.

### C. General Clinical Tests

When pulmonary and cardiovascular manifestations appear days or weeks after the initiation of the drug, a chest x-ray and electrocardiogram should be obtained. If liver or kidney involvement is suspected, liver function tests and a renal profile should be obtained. Other laboratory tests may be indicated for late hypersensitivity drug reactions. These include a complete blood count with a differential cell count and a total platelet count to exclude the possibility of cytotoxic reactions. Eosinophilia may be observed as an accompaniment of drug fever, immune complex syn-

dromes, eosinophilic pneumonias and the Churg-Strauss Syndrome. A urinalysis should be checked for the presence of proteinuria, casts, and eosinophils. Proteinuria and/or casts may denote nephropathy induced by immune complex disease or other forms of drug-induced vasculitides. The presence of urine eosinophils combined with an increase in total IgE is diagnostic of interstitial nephritis.<sup>21</sup> Other useful tests might include a sedimentation rate (or C-reactive protein), total complement or complement components, and several autoantibody tests [antinuclear antibody (ANA), antinuclear cytoplasmic antibody (c-ANCA) and peri-antinuclear cytoplasmic antibody (p-ANCA)]. A positive ANA may point to the diagnosis of the drug-induced lupus syndrome induced by drugs such as procainamide and hydralazine.<sup>37</sup> Abnormalities in c-ANCA or p-ANCA frequently occur in drug-induced systemic vasculitides and the Churg-Strauss Syndrome.<sup>38</sup> A retrospective diagnosis of anaphylaxis may be made by a rise in serum  $\beta$ -tryptase, which peaks at 1 to 2 hours and remains elevated in the serum for 2 to 4 hours (or more) after the reaction,<sup>39</sup> or a 24-hour urine for histamine and/or N-methylhistamine.<sup>40</sup> In serum sickness-like reactions, several nonspecific techniques may at times be helpful in certain situations. The most common screening test for detection of immune complexes is a test for cryoglobulins or cold precipitable serum protein. C1q binding and Raji cell assays are also available for detection of immune complexes but these are rarely necessary in the routine evaluation of drug-induced serum sickness-like reactions. Positive tests are helpful but negative tests do not exclude the possibility of immune complex disease.

### D. Specific Tests

Two criteria are used to demonstrate the immunologic basis of an adverse drug reaction: (1) detection of an immune response to the drug or its metabolite(s); and (2) demonstration that the immune response is causally related to the immunopathologic se-

quelae in an affected individual. Although an immune response to a drug is an essential component of all immunologic drug reactions, it does not prove that the patient's symptoms are due to a drug allergy. The second criterion concerning the drug's immunopathologic role in the reaction is more difficult to document. In the case of immediate hypersensitivity reactions mediated by IgE antibodies, demonstration of the presence of drug-specific IgE is usually taken as sufficient evidence that the individual is at significant risk of anaphylaxis or other immediate signs if the drug is administered. This is helpful in the case of high molecular weight agents and a few small molecular mass agents such as penicillin.<sup>41,42</sup> However, insufficient knowledge about drug degradation products and/or metabolites and how they are conjugated with body proteins has been an impediment to developing either skin or in vitro assays for most small molecular weight drug chemicals. The presence of other isotypic antibody classes or cell-mediated immunity often is poorly correlated with immunopathologic mechanisms since many individuals receiving drugs may demonstrate drug-specific immune responses but do not react adversely to the drug, even if challenged. Thus, the utility of specific immunologic tests (apart from IgE-mediated syndromes) is limited in most instances of drug hypersensitivity. At best, such tests provide adjunctive support for the clinical diagnosis.

Assessment of drug-specific IgE antibodies induced by many large molecular weight and several small molecular weight agents is often highly useful for confirming the diagnosis and prediction of future IgE-mediated reactions, such as anaphylaxis and urticaria.<sup>6,28,41</sup> Immediate type skin tests are usually the most sensitive diagnostic tests but in certain cases where skin testing is not possible (ie, a negative histamine control test, dermatographism or generalized eczema), specific IgE in vitro assays (eg, RAST, ELISA, EAST, CAP) are available but some



are not adequately standardized. In the case of small molecular weight drugs, validated and reliable skin test reagents are only available for penicillin. They have excellent negative predictive value in predicting severe reactions to penicillin. Immunoassays for penicillin-specific IgE antibodies are less sensitive than skin tests and therefore skin testing is preferred. More detailed information about the methods, reliability, and predictive capability of skin test reagents for the diagnosis of immediate drug allergic reactions may be found in "Practice Parameters for the Diagnosis and Management of Anaphylaxis" (J Allergy Clin Immunol 1998;101:S483-S484). It should be emphasized that neither immediate skin nor in vitro tests for IgE antibodies are diagnostic of cytotoxic, immune complex or cell-mediated drug-induced allergic reactions.

Both direct and indirect Coombs' tests are often positive in drug-induced hemolytic anemia. This may reflect the presence of complement and/or penicillin on the red cell membrane, or an Rh determinant autoantibody (eg, as occurs with  $\alpha$ -methyl dopa).<sup>43</sup> Sensitive drug-specific assays for IgG and IgM antibodies have been developed. Although these may be useful as diagnostic adjuncts, it is important to note that elevated levels can occur in individuals who receive the drug and do not experience a clinical reaction. Complement-dependent assays to detect drug-specific cytotoxic antibodies have also been reported. By and large, however, these tests are only available in specific research laboratories and therefore are not clinically applicable for most drugs.

The diagnosis of contact dermatitis usually can be verified by patch testing. The details of this technique are discussed in greater detail in "Practice Parameters for Allergy Diagnostic Tests" (Ann Allergy Asthma Immunol 1995;75:570-571). *In recent years there have been many reports concerning the diagnostic utility of patch tests in non-IgE mediated cutaneous drug reactions.*<sup>44</sup> *A positive reaction may be useful by identifying a specific drug in*

*a patient receiving multiple drugs, provided that it is properly compared with a group of negative controls. The lymphocyte proliferation test has been studied extensively as an in vitro correlate of drug-induced cellular reactions. This is used primarily as a retrospective test and is not clinically available in most medical centers. There is considerable disagreement among investigators about the value of this assay in evaluating drug allergies because neither its positive nor negative predictive values have been systematically investigated.* One potential advantage of the test for some patients is that it is possible to obtain in vitro evidence of lymphocyte transformation by the parent drug itself as well as liver microsomal products of the drug, thereby bypassing the need for precise knowledge of metabolic determinants.<sup>45</sup> Although the general clinical applicability of these tests has not been validated in any large scale study, a number of investigators have shown that drugs may induce both CD4+ and CD8+ T-cell responses as well as drug-specific TH-1 and/or TH-2 responses.<sup>46,47</sup> For example, certain contact sensitizers are more likely to induce TH-1 T-cell responses while a variety of systemically administered drugs may preferentially induce TH-2 responses.<sup>48</sup>

#### **E. Tissue Diagnosis**

Occasionally biopsies of involved organs may define specific histopathologic lesions. Skin biopsies are useful in differentiating vasculitis, vasculopathy, bullous diseases, and contact dermatitis.<sup>33</sup> However, they are not helpful in implicating a particular drug. A liver biopsy helps to differentiate between cholestatic and hepatocellular drug reactions but does not identify the specific cause. Membranous glomerulonephritis initiated by deposition of immune complexes in the kidney can be readily identified by immunofluorescent stains for IgG, IgM, and complement in renal biopsy specimens.<sup>49</sup> Drugs such as methicillin and sulfonamides are clearly incriminated in cases of interstitial nephritis.<sup>21</sup> Fluores-

cent antibody studies of renal biopsies in such cases reveal that these drugs bind to tubular basement membranes and may induce an immune response to bound antigen or the modified basement membrane protein.

#### **VI. MANAGEMENT AND PREVENTION OF DRUG HYPERSENSITIVITY REACTIONS**

The management of drug allergy begins with the suspicion that any unexplained rash, fever, lymphadenopathy, pulmonary, renal, gastrointestinal or other systemic disturbance may represent drug hypersensitivity. For mild reactions, a simple withdrawal of the drug may be all that is required for treatment. Acute anaphylactic reactions require the prompt administration of epinephrine; the patency of the airway should be insured and oxygen should be administered as indicated; and an intravenous cannula should be placed to facilitate administration of fluids, pressor agents, antihistamines, and glucocorticosteroids (see "Parameter for Diagnosis and Management of Anaphylaxis" J Allergy Clin Immunol 1998;101:S483-S484). Immune complex reactions usually resolve spontaneously once the antigen is cleared; however, symptomatic therapy with antihistamines and possibly non-steroidal inflammatory drugs (NSAIDs) may be indicated for control of urticaria<sup>50,51</sup> and joint symptoms, respectively. In cases complicated by more severe symptoms, refractory urticaria or vasculitis, treatment with glucocorticosteroids is indicated. Glucocorticosteroids may also be required for the treatment of drug-induced hemolytic, thrombocytopenic or granulocytic cytopenias, especially in situations where the responsible drug must be continued as a life saving measure.<sup>52</sup>

Allergic drug reactions or a history of such reactions are occasionally encountered in other clinical situations where continued use of the drug is imperative. Among the most important conditions where drug use may be justified are diabetic ketoacidosis, bacterial endocarditis, inflammatory bowel

disease, neurosyphilis, AIDS, and pulmonary tuberculosis. When no alternative drug is available for therapy, the risk of continued administration of the offending drug may be less than the risk to life posed by the underlying disease. Where there is a definite medical indication for the agent in question, either desensitization or graded challenge procedures may be considered, depending on the history of the previous reaction. The use of suppressive drugs is optional. These protocols require the supervision of an allergy/immunologist having previous experience with these procedures (see "Practice Parameters for the Diagnosis and Management of Anaphylaxis" *J Allergy Clin Immunol* 1998;101:S465–S528).

Specific desensitization is the rapid progressive administration of an allergenic substance to render effector cells less reactive. Such procedures vary with individual drugs and they are successful chiefly with agents that induce IgE-mediated reactions. For example, in the case of penicillin, the initial desensitization dose is usually 100 to 1000 times lower than the concentration of the drug which produced a positive skin test. Oral desensitization may be less likely to induce anaphylaxis than parenteral administration.<sup>53</sup> Further dosage increases are given at 15 to 30-minute intervals until therapeutic levels are achieved. In most cases this can be accomplished within 4 to 5 hours. This regimen should be reserved for hospitalized patients, requiring that experienced personnel and resuscitation equipment be available at all times. Desensitization programs are available for a variety of drugs including penicillin, a number of non-beta lactam antibiotics and insulin. Even if formal protocols do not exist, desensitization can be attempted with other agents.

A graded challenge regimen (see glossary for definition) may be attempted to confer clinical tolerance to drugs associated with a variety of non-IgE hypersensitivity reactions.

The principle of a graded challenge is based on the administration of small doses of the drug with incremental progression at regular intervals until a therapeutic dose is achieved.<sup>54</sup> The most common drugs in this category are para-aminosalicylic acid, isoniazid, TMP-SMX, pentamidine, dapsone, allopurinol, sulfasalazine, diphenylhydantoin, and penicillamine. A 6-hour graded challenge to TMP-SMX in HIV-infected patients has proven to be successful without major long term complications.<sup>55</sup> Graded challenge with aspirin (ASA) or NSAIDs is also possible in patients who are intolerant to these drugs, particularly for those with respiratory reactions.<sup>56</sup> Initial doses are higher than desensitization (mg versus  $\mu\text{g}$ ) and the interval between dose increments are variable, ranging from hours, days, or weeks. Modified, more cautious regimens are based on the fact that slower readministration may be more likely to reveal systemic intolerance, which can be recognized early enough to prevent progression to life-threatening erythema multiforme major/Stevens-Johnson syndrome and/or the toxic epidermal necrolysis syndrome induced by some of these drugs. Future use of drugs which cause these syndromes as well as other life-threatening conditions (eg, Churg-Strauss syndrome and exfoliative dermatitis) is absolutely contraindicated.

Slow graded challenge of a drug in increasing amounts over days or weeks may be required for inducing tolerance to drugs causing non-IgE-mediated skin rashes. This technique may offer another approach to a previously unsuccessful rapid graded challenge regimen (eg, hours to days for drugs such as trimethoprim-sulfamethoxazole, sulfasalazine, and allopurinol).<sup>57</sup>

Cautious use of some agents inducing pseudoallergic reactions (eg, radiocontrast dyes) is often possible by pretreatment of patients with glucocorticosteroids,  $H_1$  (with or without  $H_2$ ) antihistamines and/or albuterol/ephedrine (see "Practice Parameters On Diagnosis and Management of Anaphylaxis"

*J Allergy Clin Immunol* 1998;101: S503–S504).

Prevention of allergic drug reactions is more desirable than treatment of reactions once they occur. The majority of serious allergic drug reactions can be prevented or at least attenuated by alert management. Patients should be questioned directly concerning previous drug reactions and medical records should be reviewed for previous notations of drug allergy. Cross-reactivity between chemically related drugs should be anticipated. Drugs known to produce adverse reactions frequently (eg, antibiotics) should be prescribed only for valid indications and combinations of drugs should be used sparingly. Orally administered drugs are less likely to produce reactions than drugs given by the topical or parenteral route. If injectable drugs are administered, epinephrine and other emergency measures for treatment of acute anaphylaxis should be available. Medic-Alert tags and bracelets represent a useful way of alerting physicians to a previous severe allergic reaction, although it should be kept in mind that historical diagnoses of drug allergy often are erroneous or tenuous.

Skin tests may be predictive of risk in certain instances, especially with penicillin, heterologous sera, and insulin.<sup>9,14</sup> The frequency with which heterologous sera are prescribed for humans has declined, resulting in a decrease in the number of anaphylactic or serum sickness reactions to these agents. Further, homologous sera are now available for passive immunization against tetanus, hepatitis B, and rabies.

A few states now require that the names and concentrations of all medications appear on prescription labels. This is a useful advance which helps to assure that the patient is being educated about prescribed medications. In addition, the routine establishment of individual patient drug profiles by some hospitals and commercial pharmacies facilitates identification of potential allergic reactions.

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## VII. PROTOTYPES OF IMMUNOLOGICALLY MEDIATED DRUG HYPERSENSITIVITY

Almost any drug is capable of inducing an allergic reaction and the likelihood that this will occur increases in direct proportion to the usage pattern of a drug in the general population. Drugs differ, however, with their propensities to induce either restricted or heterogeneous immune responses within the Gell-Coombs spectrum of human hypersensitivity. This section will discuss several of the most common clinical entities of drug hypersensitivity, some as representative examples of each of the four major Gell-Coombs' categories of human hypersensitivity and others with heterogeneous and often unclassifiable immune characteristics.

### A. IgE-Mediated Reactions (Gell-Coombs Type 1)

IgE-mediated hypersensitivity reactions may occur after administration of a wide variety of drugs, biologicals, and drug formulation agents. The most important drug causes of immediate hypersensitivity reactions are antibiotics. Other common drugs that cause such reactions are insulin, enzymes (streptokinase and chymopapain), heterologous antisera (equine antitoxins and, antilymphocyte globulin), murine monoclonal antibodies, protamine, and heparin.<sup>58-64</sup> Detailed discussions about these agents may be found in the "Practice Parameters for the Diagnosis and Management of Anaphylaxis" J Allergy Clin Immunol 1998;101: S505-S515). Allergic Type 1 reactions also have been reported after exposure to excipients such as eugenol, carmine, vegetable gums, paraben, thiomerosal, sodium metabisulfite, formaldehyde, and sulfonechloramide.<sup>13</sup> In the following discussion, we will consider both beta lactam and non-beta lactam antibiotics as the major prototypes in this category.

#### 1. Beta lactam antibiotics

Anaphylactic reactions manifested by urticaria, flushing, pruritus, laryngeal edema, and cardiovascular collapse

may occur within minutes or, less frequently, hours after administration of beta lactam antibiotics (ie, drugs that have a common beta lactam ring structure). Drugs in this category include penicillin, semi-synthetic penicillins (eg, amoxicillin), cephalosporins, carbapenems (eg, imipenem), monobactams (eg, aztreonam), and carbacephems. In addition, non-IgE mediated immunologic reactions may also be caused by this class of drugs. These include: cytopenias, immune complex disease such as serum sickness, vasculitis, glomerulonephritis, fever, and non-urticarial rashes.

**Penicillin.** The prevalence of penicillin hypersensitivity in the general population is not known. Up to 10% of hospitalized patients have been reported to give a history of allergy to penicillin and, for this reason, many of these patients receive alternative antimicrobial drugs.<sup>65</sup> The frequency of anaphylaxis is estimated to be 0.01% to 0.05% with each course of penicillin.<sup>32</sup> The nature of the past reaction correlates somewhat with the chance of being allergic to penicillin but history alone is not sufficiently reliable to make a diagnosis of penicillin hypersensitivity. Thus, over 80% of patients with a past history of penicillin hypersensitivity do not have penicillin-specific IgE antibodies detected by skin testing.<sup>66</sup> Although many patients with documented hypersensitivity to penicillin lose sensitivity with time, about 20% may maintain their hypersensitivity status for long periods of time. Up to 46% of patients with a history of anaphylaxis and about 15% of those with a history of urticaria and angioedema will exhibit positive immediate hypersensitivity skin tests to penicillin when tested at a later date.<sup>67</sup> The most reliable method for evaluating IgE-mediated penicillin allergy is by skin testing to both major and minor determinants of penicillin. Positive commercial in vitro tests (RAST or ELISA) may suggest a diagnosis of penicillin allergy. Negative commercial tests, however, are not reliable for excluding penicillin hypersensitivity because they are relatively insensitive and do not test for minor de-

terminants.<sup>68</sup> Although skin testing predicts only the risk of developing an IgE-mediated reaction, this information is of critical clinical importance because most life threatening reactions to penicillin are the result of IgE-mediated anaphylaxis.

If possible, it is preferable to treat a patient with a history of penicillin allergy with a non-beta lactam antibiotic that is equally efficacious. Many alternate antibiotics, however, may be less effective, more expensive, or associated with more side effects than penicillin. If there is no effective alternative, an allergist/immunologist should be consulted to determine whether the patient is allergic to penicillin. Ideally, skin tests should be performed immediately prior to planned administration of penicillin. In penicillin history-positive patients, testing is safe provided the recommended skin test procedure is followed.<sup>42,67,69-71</sup> Penicillin skin testing is not predictive of: (1) IgG or IgM-mediated immune complex disease (eg, serum sickness, glomerulonephritis, or vasculitis); (2) hemolytic anemia; (3) erythema multiforme minor, erythema multiforme major/ Stevens-Johnson syndrome; or (4) toxic epidermal necrolysis. There is no way to adequately predict these non-IgE immune reactions and therefore, patients with a history of these reactions should never receive penicillin again. It appears safe to skin test and rechallenge patients with a history of isolated drug fever.<sup>36,42</sup> Skin testing should be postponed in anyone currently receiving antihistamines or antihistamine-like drugs until the respective drug is discontinued and the histamine wheal and flare responses is re-established.

A negative skin test to both major and minor determinants performed within days of a planned therapeutic course of penicillin means that a patient may receive penicillin without significant risk of an IgE-mediated reaction. Although there has been concern that skin test reagents might stimulate specific IgE production, re-sensitization as a result of skin tests to both major and minor determinants of penicillin has not been demonstrated. A negative penicillin

skin test could possibly later convert to positive if the patient has a hidden exposure to penicillin between the time of the negative skin test and later administration of the drug. While this conversion could occur, especially among medical personnel exposed to penicillin, it appears to be a rare event.

Because of the frequent outpatient need for penicillin treatment in the pediatric population and the impracticality of testing children when sick, testing them when they are well and not in immediate need of penicillin may be considered.<sup>70</sup> Although it is preferable to perform skin testing when there is an immediate need for penicillin, there may be some situations where skin testing of history positive adults not in immediate need of treatment may also be indicated. These include: (1) patients with a history of mitral valve prolapse or other disorders, which require amoxicillin prophylaxis before dental work, and who are unable to take erythromycin, azithromycin, or other appropriate antibiotics; (2) cancer chemotherapy-induced neutropenia in patients who might require penicillin promptly for infections that appear suddenly; or (3) patients with a recent possible IgE-mediated penicillin reaction in order to confirm the cause.

A positive skin test identifies patients who have penicillin-specific IgE antibodies and may be at risk of an immediate life-threatening reaction if given penicillin. This reaction includes hypotension, urticaria, laryngeal angioedema, flushing, or pruritus and may occur within minutes or hours after administration. Skin testing does not predict the development of IgE-mediated reactions which may begin 24 hours or more after penicillin administration or reactions due to other "mixed" immune mechanisms (ie, IgM, IgG, or T cell-mediated reactions). If skin testing to the major and minor determinants of penicillin is negative, 97% to 99% of patients (depending on reagents used) will tolerate penicillin administration at the time of testing without risk of an immediate reaction.<sup>42</sup> Therefore, the negative predictive value is very high.<sup>42</sup> A mixture

of minor determinants is not commercially available. If penicilloyl polylysine (major determinant) and penicillin G are used for skin testing, 97% of patients with a negative skin test will tolerate penicillin.<sup>71</sup> Another combined prospective/retrospective study revealed that 99% of these patients tolerated penicillin.<sup>72</sup> Nevertheless, sensitivity to one of the minor determinants lacking in penicillin G may not be detected if this reagent is used for skin testing. In this regard, 7% to 17% of skin test positive patients have demonstrated reactivity to a minor determinant other than penicillin G.<sup>66</sup> This may not be clinically important because reaction rates were low in a large number of challenged penicillin G skin test negative patients.<sup>71,72</sup> If a patient has both a positive history and a positive skin test for penicillin allergy, there is a 50% or greater chance of an immediate reaction if penicillin is given. The precise positive predictive value has not been determined because of the risk associated with deliberate challenge in skin test positive patients.

In the case of a positive history, skin test-negative patient who tolerates a therapeutic course of penicillin, the predictive value of the skin tests for future therapeutic courses of penicillin is unknown.<sup>67,68</sup> The resensitization rate appears to be higher in adults than children.<sup>73</sup> In the situation where the original history was consistent with a severe IgE-mediated anaphylactic reaction, the patient tolerated a course of penicillin and the drug has to be readministered, it has been suggested that retesting should be considered or the patient could undergo a test dose challenge.<sup>74</sup> *For history-positive skin test negative patients who tolerate two courses of penicillin therapy without reaction, the likelihood that a conversion to a skin test positive state is extremely low and it is not necessary to perform skin testing or graded challenge prior to additional courses of therapy.*

Penicillin skin testing is best performed by personnel skilled in performing and in interpreting immediate hypersensitivity skin tests to drugs.

The techniques, controls, and interpretation are also discussed in "Practice Parameters of Allergy Diagnostic Tests" Ann Allergy Asthma Immunol 1995;75:586). Skin testing should be done with (1) benzyl penicilloyl, the major determinant of penicillin, commercially available as PrePen and (2) penicillin G diluted to 10,000 units/mL or a mixture of minor determinants (MDM; not commercially available) which usually includes a  $10^{-2}$  M mixture of benzyl penicilloate, benzyl penilloate, and benzyl-n-propylamine.<sup>75-77</sup> Benzyl penicilloyl (PrePen) can be used directly from commercial vials. Penicillin G is stable for 1 week refrigerated at a concentration of 100,000 units/mL and for 6 months, if frozen. Diluted skin test reagents should be used within 24 hours.<sup>78</sup> *If full strength prick tests (Pre-Pen  $6 \times 10^{-5}$  M, MDM  $10^{-2}$  M or penicillin G 10,000  $\mu$ /mL) are negative, full strength intracutaneous tests may be placed. Some practitioners feel that more cautious titration with 10-fold to 100-fold dilutions of prick and/or intracutaneous tests should be employed.<sup>42,79,80</sup> Wheal sizes  $\geq 3$  mm and erythema greater than the negative control are considered positive for both prick and intracutaneous tests.*

Using these reagents and proper technique, serious reactions from penicillin skin testing are extremely rare. Anaphylactic reactions and deaths from penicillin skin testing have been reported but all were due to administration of higher doses initially or intracutaneous testing not preceded by prick/puncture testing. Use of penicillin skin test reagents does not appear to resensitize the patient. If a systemic reaction to a skin test occurs, patients on concurrent beta-adrenergic blocking agents or angiotensin converting enzyme inhibitors at the time of skin testing may not respond to emergency treatment with epinephrine. For more detailed information about this issue, refer to "Practice Parameters on Diagnosis and Management of Anaphylaxis" J Allergy Clin Immunol 1998; 191:S484).

If skin testing is positive to any penicillin reagent, the patient should re-

ceive an alternate antibiotic, unless penicillin is essential. In that case, the patient should undergo desensitization. If the skin test is negative, the patient may receive penicillin. An oral subtherapeutic test dose may be given before the full recommended dose. If penicillin G is used as a substitute for the MDM reagent, there is a small risk that IgE antibodies to minor determinants not present in the penicillin G may not have been detected. For these skin test-negative patients, a test dose of approximately 1/100th of the desired therapeutic dose of penicillin should be administered first. If no reaction occurs (eg, within 60 minutes), the full dose may be given safely in most cases. If such a patient experiences a significant reaction within 1 hour of exposure, a formal desensitization protocol may be considered.

**Ampicillin and amoxicillin.** Administration of ampicillin and amoxicillin is associated with the development of a maculopapular rash in 5% to 10% of patients.<sup>81</sup> These patients are not at risk of a life threatening reaction to penicillin. Most patients will tolerate future administration of penicillin other than ampicillin and amoxicillin without reactions of any kind. If ampicillin or amoxicillin is administered again, the patient could redevelop a rash, but rarely a non-dermatologic reaction. Re-administration of ampicillin or amoxicillin may be better tolerated by children than by adults. If patients with Epstein-Barr infections are given ampicillin or amoxicillin, almost 100% will develop a non-pruritic rash.<sup>82</sup> The incidence of non-pruritic, cutaneous reactions also may be increased in patients who have an elevated uric acid, are being treated with allopurinol, or have chronic lymphocytic leukemia.<sup>83,84</sup> If the rash to ampicillin or amoxicillin is other than maculopapular and non-pruritic in nature (eg, urticarial), the patient should undergo penicillin skin testing before a future course of penicillin is given. If penicillin skin testing is negative, the patient should be approached as outlined in the prior discussion about penicillin. If penicillin skin testing is positive, the

patient should be given an alternative antibiotic or undergo desensitization to penicillin.

**Cross-reactivity between carbapenems, monobactams, ampicillin and penicillin.** Carbapenem (eg, imipenem) should be considered cross-reactive with penicillins.<sup>85</sup> The monobactam aztreonam does not appear to cross-react<sup>86,87</sup> with penicillins but anecdotal episodes of anaphylaxis have been reported.<sup>88</sup> There are instances where antibodies specific for penicillin side chains may exist in the absence of beta lactam-specific antibodies.<sup>89-91</sup> Patients in this category probably include those with positive skin tests to ampicillin but negative to penicillin. Not all these patients have been prospectively challenged so the clinical significance of these side chain-specific antibodies is as yet unclear.

**Cephalosporin allergy** (see cephalosporin algorithms p 687). Cephalosporins and penicillins have a common beta-lactam ring structure and moderate cross-reactivity has been documented in vitro. Although clinically significant cross-reactivity between penicillin and the cephalosporins is infrequent, anaphylactic reactions after administration of cephalosporin have occurred in patients with a positive history of penicillin anaphylaxis.<sup>92</sup> Most of the in vitro cross-reactions between penicillins and cephalosporins have involved first and second generation cephalosporins.<sup>93,94</sup> While IgE antibodies to the beta lactam ring of penicillin are of major importance, some reactions to cephalosporins may not be directed to the beta lactam ring and may be side chain specific.<sup>89,93</sup> Skin testing with a cephalosporin is not necessary if the patient has a history of allergy to penicillin, but has tolerated a cephalosporin safely since the original penicillin reaction.<sup>66</sup> Allergy to cephalosporins is uncommon compared with penicillin allergy. *If a patient with a past history of allergy to one cephalosporin agent requires another cephalosporin, the following can be considered: (1) after insuring that the new cephalosporin does not share side chain determinants with the original one, perform a graded challenge with*

*the new one; or (2) cephalosporin skin testing can be done although such skin testing is not standardized and the negative predictive value is unknown.* The cephalosporin currently required should be used as the skin test reagent. Concentrations of 3 mg/mL of a parenteral preparation are usually non-irritating but each cephalosporin requires concurrent evaluation for its irritation potential in non-allergic patients. Skin testing should be done as described in the penicillin section with a prick/puncture test at 3 mg/mL concentration followed by an intracutaneous test (if the prick-test reaction is negative in 10 to 15 minutes). If the previous clinical reaction was documented as anaphylactic and life-threatening, testing should start at 0.3 mg/mL or lower. A positive cephalosporin skin test implies the presence of drug-specific IgE antibodies and the patient should receive an alternate drug or undergo desensitization. Although a negative skin test at an intracutaneous concentration of 3 mg/mL may imply that the patient does not have detectable drug-specific IgE antibodies, it does not ensure that drug-specific antibodies are absent. IgE antibodies to cephalosporin degraded products not used in the testing may be present but not detectable. Since the negative predictive value of cephalosporin skin testing is unknown, a cautious graded challenge should be done (eg, 1/100 of the therapeutic dose, increasing tenfold every 30 to 60 minutes up to the full therapeutic dose). However, if the previous history was consistent with an IgE-mediated reaction, desensitization should be undertaken.

**Administration of cephalosporin to patients with a history of allergy to penicillin (see algorithm p 687).** Prior to 1980, penicillin history-positive, skin test-positive patients who were given cephalosporin had a reaction rate of approximately 10% to 20%. Since 1980, reaction rates in penicillin history-positive, skin test-positive patients who were given a cephalosporin have decreased to 2%.<sup>66</sup> Prior to 1980, all penicillin-allergic patients who have reacted to a cephalosporin

had been treated with cephalothin or cephaloridine. Benzyl penicillin and these first generation agents share a similar side chain, a finding that could account for increased cross-reactivity. Also, during this time, some early first generation cephalosporins were contaminated with trace amounts of penicillin. Since 1980, contamination of this type has not been documented. *Nevertheless, because of these disparate observations, there is not a common consensus regarding the management of a patient with a good history of an IgE-mediated reaction to penicillin and who subsequently requires administration of cephalosporin. The following are options that may be considered (1) substitute a non-beta lactam antibiotic and (2) skin test the patient to determine whether the patient has IgE antibodies to penicillin. If the skin test is negative, the patient can receive the cephalosporin. If the skin test is positive, there may be an increased risk of a reaction if the cephalosporin is given and desensitization with the cephalosporin should be performed.*

If patients with histories of allergy to penicillin are not skin tested but given a second or third generation cephalosporin directly, the chance of a reaction is probably less than 1%.<sup>94</sup> This figure is based on the fact that only 15% to 20% of penicillin history-positive patients have positive skin tests and, of those, only 2% will react to a cephalosporin.<sup>95</sup> This finding may be interpreted to mean that skin testing is unnecessary as a 2% reaction rate may occur even without a prior history of allergy. It should be emphasized, however, that most of the 2% reactors were cases of anaphylaxis, some of which were fatal.<sup>92</sup> For this reason, it is recommended that penicillin skin test-positive patients should undergo a formal cephalosporin desensitization regimen.

**Administration of penicillin to a patient with a history of allergy to a cephalosporin.** Patients with a history of an immediate-type allergic reaction to a cephalosporin who require penicillin should undergo penicillin skin testing. If negative, they can receive

penicillin; if positive, they should receive an alternate drug or undergo penicillin desensitization. If the patient has a history of a non-IgE-mediated reaction to cephalosporin [other than erythema multiforme major/Stevens-Johnson syndrome (EMM/SJS) or toxic epidermal necrolysis (TEN)] and requires one of the cephalosporins, the patient can undergo a graded challenge. Skin testing with penicillin is not appropriate in this setting.

**Cross-reactivity between carbapenems, monobactams and cephalosporins.** Carbapenems (eg, imipenem) should be considered potentially cross-reactive with cephalosporins because of the beta lactam ring.<sup>85</sup> Cross-reactions between monobactams (eg, aztreonam) and cephalosporins have not been demonstrated, except for ceftazidime which has a side chain identical to that of aztreonam.<sup>87,88</sup>

## 2. Non-Beta Lactam Antibiotics

Allergic reactions to non-beta lactam antibiotics can cause morbidity and, rarely, mortality. The overall incidence of hypersensitivity reactions to these agents is estimated to be 1% to 3%. Some agents such as TMP-SMX are more prone to induce such reactions, particularly in HIV-infected individuals.<sup>96-98</sup> Administration of a different antibiotic may sometimes be necessary in a patient whose history is consistent with an allergic reaction to that non-beta lactam antibiotic. If the non-beta lactam antibiotic is needed urgently and the history is consistent with an IgE-mediated reaction, desensitization may be required if an alternative drug is not available. If the drug is not needed urgently and the history is consistent with a non-IgE-mediated mechanism, cautious graded challenge sometimes on an outpatient basis can generally be conducted.

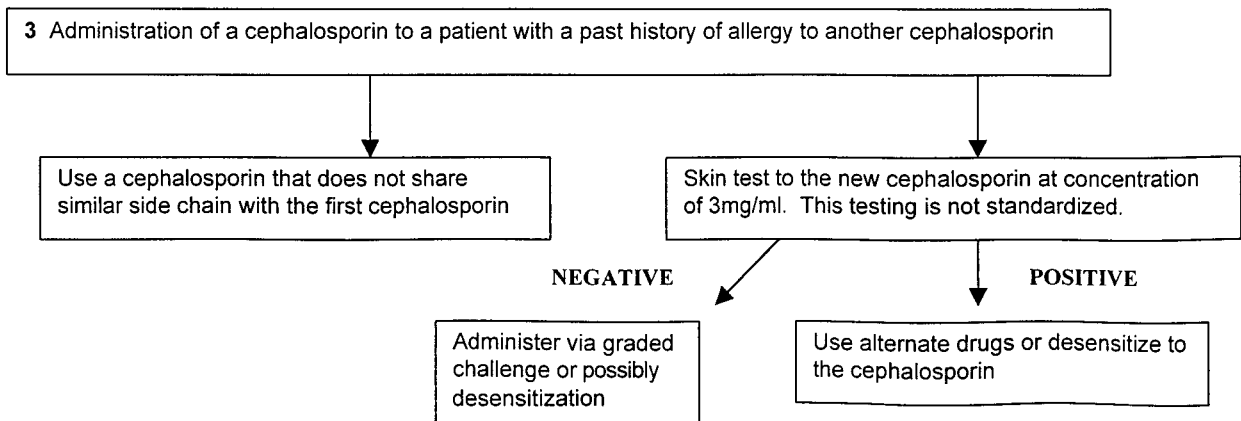
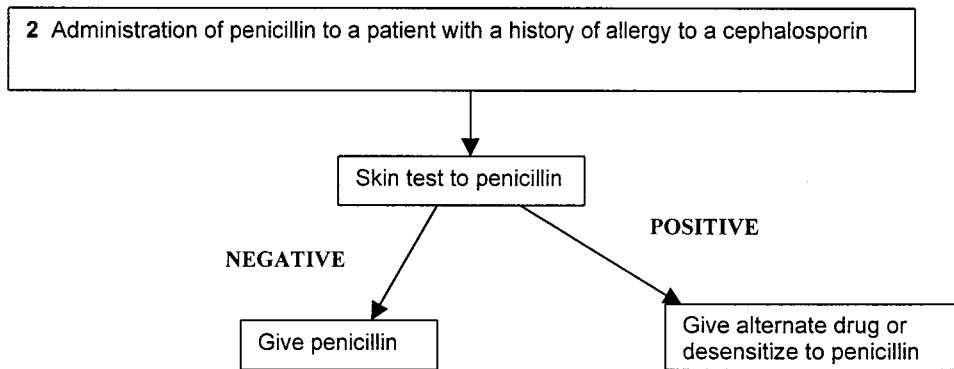
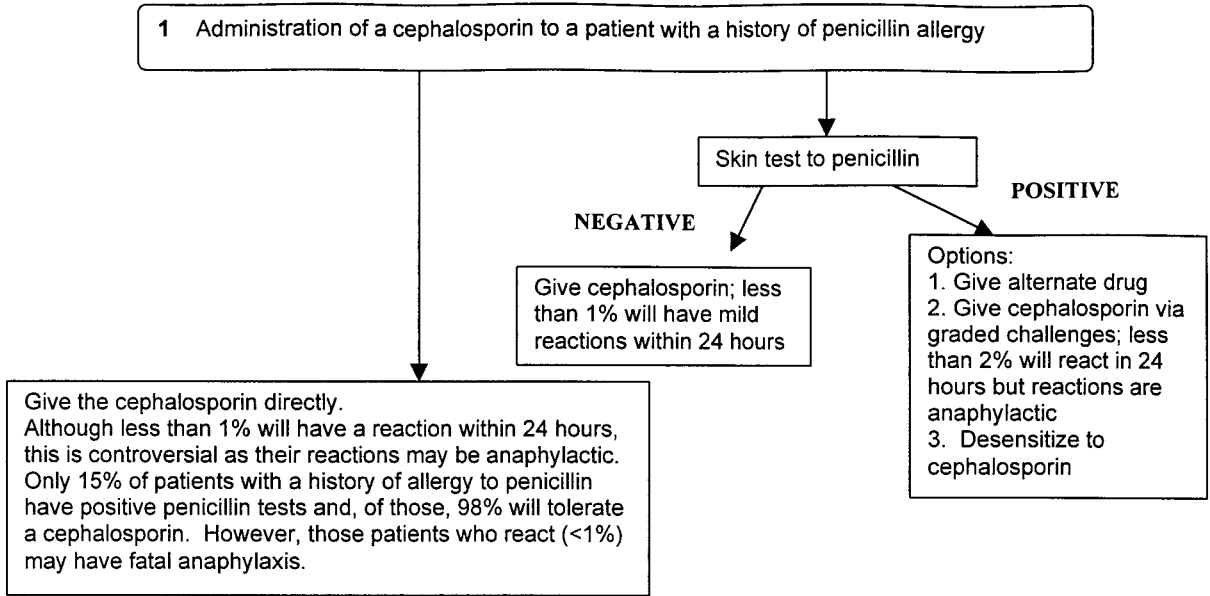
In the case of some antibiotics, there are case reports of positive skin tests with the native drug; however, large scale validation of such skin testing has not been accomplished. It is well recognized that most antibiotics have multiple end products and therefore it is possible that the relevant allergens

may be metabolites and not the parent drug. While no validated in vivo or in vitro diagnostic tests are available for non-beta lactam antibiotics, skin testing with nonirritative concentrations of the drug (ie, negative skin test reactivity in a panel of normal, nonexposed volunteers) may provide useful information. If the skin test is positive under these circumstances, it is likely that drug-specific IgE antibodies are present. The patient should therefore receive an alternative antibiotic or undergo desensitization. On the other hand, a negative test does not denote that drug-specific IgE antibodies are absent, since it is possible that a drug metabolite not present in the test reagent may be the relevant allergen. If this particular antibiotic is required for treatment, the amount of drug injected intracutaneously can be used as the initial starting dose for a desensitization procedure. Graded test dosing challenge can also be performed in patients with a history that suggests a non-IgE-mediated reaction other than EMM/SJS or TEN. In general, for oral agents the starting dose is 0.1 mg. Incremental doses can be administered every 30 to 60 minutes (eg, 1 mg, 10 mg, and 50 mg) until a full therapeutic dose has been achieved.

A generalized maculopapular reaction is the most common manifestation of drug allergy due to TMP-SMX in patients with AIDS. Many such patients can tolerate readministration of the drug if given slowly over hours or days. In severely ill patients, particularly those with *Pneumocystis carinii* pneumonia, more rapid administration may be necessary. A detailed discussion of TMP-SMX is presented in section X, Adverse Drug Reactions in Patients with HIV Infections/AIDS (p 694).

Vancomycin has been reported to cause drug fever, skin rash, or a distinctive cutaneous lesion, the "red man's syndrome" characterized by pruritus; erythema; and flushing of the face, neck, and upper throat; and sometimes hypotension. Prospective studies have noted that 50% to 90% of treated patients experience some of these man-

Figure 1. Cephalosporin algorithms.



ifestations, although most of them are mild. These symptoms are due to non-specific histamine release that is rate related, so that slowing the rate of infusion will generally prevent further symptoms. Addition of an H<sub>1</sub> antihistamine also helps to alleviate symptoms.<sup>99</sup> IgE-mediated anaphylaxis to vancomycin has also been observed and may be identified by skin tests but it should be noted that skin tests at concentrations  $\geq 100 \mu\text{g}$  may elicit "false positive" wheal and flare reactions in normal skin. Anaphylaxis should be managed in the same manner described for other non-beta lactam antibiotics.<sup>100</sup>

Although aminoglycosides rarely cause hypersensitivity reactions, there are individual case reports of IgE-mediated systemic reactions.<sup>101</sup> Desensitization is sometimes indicated when the drug allergy is thought to involve IgE antibodies and no alternative antibiotic is available. Both graded challenge and desensitization procedures should be performed by specialists experienced with these protocols and the possible adverse events associated with them.

Quinolones (eg, ciprofloxacin) are a class of antibiotics related to nalidixic acid. Anaphylactoid reactions to this class of drug, often following the initial dose, have been reported.<sup>102</sup> Cutaneous lesions appear in about 2% of treated patients.<sup>103</sup> Patients reacting to one quinolone are likely to react to related drugs of this class.<sup>104</sup>

### **B. Cytotoxic Reactions (Gell-Coombs Type 2)**

Cytotoxic reactions are very serious and potentially life-threatening. Immunohemolytic anemias due to drugs have clearly been identified after treatment with quinidine,  $\alpha$ -methyl dopa and penicillin. In the case of penicillin, circulating anti-penicillin antibodies of the immunoglobulin G isotype have been implicated.<sup>9</sup> The condition is rare because it apparently develops only in those individuals capable of synthesizing an atypical variety of IgG anti-penicillin antibody. Penicillin binding by erythrocytes is an essential preliminary step in the sensitization process

and is more likely to occur in patients receiving very large and prolonged dose regimens of penicillin, as may be required in the long-term treatment of subacute bacterial endocarditis. As previously discussed, positive direct and indirect Coombs' tests in this condition also may indicate the presence of complement on the red cell membrane or an autoantibody to an Rh determinant.<sup>43</sup>

Thrombocytopenia resulting from drug-induced immune mechanisms has been well documented. The most thoroughly evaluated drugs in this category are quinine, quinidine, acetaminophen, propylthiouracil, gold salts, and the sulfonamides. Platelet membrane damage is mediated chiefly by circulating drug-immune serum complexes which are absorbed onto platelet membranes.

Granulocytopenia also may be produced by cytotoxic antibodies synthesized in response to such drugs as pyrazolone derivatives, phenothiazines, thiouracils, sulfonamides, and anti-convulsives. Immunologically mediated destruction of peripheral neutrophils occurs within minutes after readministration of the drug and the immunologic specificity of the antibody has been verified by passive transfer to nonsensitive volunteers (in the pre-AIDS era).<sup>14</sup>

### **C. Immune Complex Reactions (Gell-Coombs Type 3)**

Serum sickness was originally noted when heterologous antisera were used extensively for passive immunization of infectious diseases. Many small molecular weight drugs are also associated with serum-sickness-like symptoms. These include penicillin, sulfonamides, thiouracils, and phenytoin. The chief manifestations of fever, rash, urticaria, lymphadenopathy, and arthralgias typically appear 1 to 3 weeks after the last dose of an offending drug and begin to subside when the drug and/or its metabolites are completely eliminated from the body.<sup>34</sup> Most of the clinical symptoms are thought to be mediated by IgG and possibly IgM-drug complexes. The overall immune response in immune complex reactions

is heterogeneous because in some cases, IgE antibodies can also be demonstrated and may be associated with urticarial lesions seen early in the course of the disease.

### **D. Cell-Mediated Reactions (Gell-Coombs Type 4)**

Allergic contact dermatitis after exposure to medications containing active drugs, additives, or lipid vehicles in ointments is the most frequent form of drug-mediated delayed hypersensitivity. Morphologically, it usually cannot be distinguished from contact irritant dermatitis. Almost any drug applied locally is a potential sensitizer but less than 40 allergens produce most cases of contact dermatitis. Among the drugs involved, the most universally accepted offenders are topical formulations of penicillin, local anesthetics, and antihistamines. Potent excipient topical sensitizers include the parabens, formaldehyde, ethylenediamine, lanolin, and thimerosal.<sup>105</sup> Complex topical products may contain many potential antigens and additives and in many instances the major component of a complex mixture may not necessarily be the sensitizer. Photoallergic dermatitis morphologically resembles allergic contact dermatitis and is caused by such drugs as sulfonamides, thiazides, quinidine, chlorpromazine, and fluoroquinolones. Once induction sensitization has occurred, elicitation of dermatitis requires minimal exposure to light. Phototoxic, non-allergic reactions (eg, erythrosine) are histologically similar to photoallergic inflammatory responses. As previously discussed, T-cell mediated mechanisms (ie, CD8<sup>+</sup> T cells) have been demonstrated in patients with late onset cutaneous reactions such as morbiliform and bullous eruptions.<sup>6,7</sup>

### **E. Miscellaneous Syndromes**

Specific drugs or classes of drugs are associated with characteristic syndromes which often do not conform with specific Gell-Coombs categories. Although various specific immune phenomena can often be demonstrated in these syndromes, their roles in the



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immunopathogenesis of the disease have not been clearly established.

*I. Drug Reactions Associated with Specific Reactive End Products/Metabolites or Pharmacogenetic Polymorphisms*

Although reactive metabolites may exert non-immune toxic effects, they may also haptenate body proteins to initiate various immunopathogenetic effects. Immunoreactivity has been identified with some drug reactions in this category, but mixed mechanisms including direct toxicity cannot be entirely excluded.<sup>6</sup>

**Hypersensitivity vasculitis.** Many agents, hematopoietic growth factors, cytokines, and the interferons are suspected of causing widespread vascular inflammation of skin and visceral organs.<sup>38,106</sup> Frequently, the vascular changes occur during the course of or at the endstage of drug-induced syndromes of serum sickness or drug fever. Drugs such as hydralazine, anti-thyroid medications, minocycline, and penicillamine are often associated with c-ANCA or p-ANCA-positive vasculitis-like disease. Antinuclear cytoplasmic antibody positive vasculitis is also associated with hydralazine-induced systemic lupus erythematosus. Similar findings also apply to propylthiouracil. Procainamide, an anti-arrhythmic agent, is the drug most commonly associated with drug-related lupus.<sup>107</sup> Lupus-like features occur in 15% to 30% of these patients and a large array of immune and autoimmune disturbances has been reported. A Henoch-Schönlein syndrome with cutaneous vasculitis and glomerulonephritis may be induced by carbidopa/levodopa.<sup>108</sup>

**Anti-Convulsant hypersensitivity syndrome.** This life-threatening syndrome may occur after varying periods of exposure to anticonvulsant medications. It appears to result from an inherited deficiency of epoxide hydrolase, an enzyme required for the metabolism of arene oxide intermediates produced during hepatic metabolism of anticonvulsant drugs. It is characterized by fever, a maculopapular rash and generalized lymphadenopathy

and resembles the progression of symptoms that occur during a serum-sickness-like reaction.<sup>109</sup> Physical signs tend to persist for some time after the drug is discontinued. Biopsies of lymph nodes in this condition are sometimes confused with Hodgkin's disease and the entire syndrome has therefore been called "pseudolymphoma." Hepatitis, nephritis, and leukocytosis with atypical lymphocytes and eosinophils may be part of the syndrome. Facial edema occurs in 25% of the patients. These multi-organ reactions may be induced by phenytoin, carbamazepine, or phenobarbital and cross-reactivity may occur among all anticonvulsants that produce toxic arene oxide metabolites. Valproic acid, gabapentin, and lamotrigine may be acceptable therapeutic alternatives since none of these agents produce arene oxide.

**Pulmonary drug hypersensitivity.** Pulmonary manifestations of allergic drug reactions include anaphylaxis, lupus-like reactions, alveolar or interstitial pneumonitis, edema, granulomatosis, and fibrosis.<sup>110</sup> Acute pneumonitis with fever, rash, and eosinophilia occurs after treatment with nitrofurantoin, NSAIDS, and sulfasalazine. If the drugs are not eliminated promptly, these lesions may progress to a chronic course with interstitial fibrosis. Biopsy-proven eosinophilic pneumonia may occur after use of sulfonamides, penicillin, and para-aminosalicylic acid. Patchy pneumonitis, pleuritis and pleural effusion may appear during the course of various drug-induced lupus syndromes.<sup>37,107</sup> Whether or not pleuropulmonary fibrosis has an immunologic basis is unknown at the present time. Characteristic histologic fibrotic changes are caused by certain cytotoxic drugs such as bisulphan, cyclophosphamide, and bleomycin. Acute pulmonary reactions produced by other fibrogenic drugs, such as methotrexate, procarbazine, and melphalan are similar to those of nitrofurantoin pneumonitis and therefore appear to be mediated by hypersensitivity mechanisms. These lesions are sometimes confused with noncardiac pulmonary edema

which occurs after administration of heroin, methadone, propoxyphene, or hydrochlorothiazide. The clinical spectrum of pulmonary hypersensitivity reactions may include interstitial pneumonitis (with or without eosinophilia), bronchiolitis obliterans [with or without organized pneumonia (BOOP)], the pulmonary-renal syndrome associated with penicillamine, and granulomatous lesions.<sup>110,111</sup> The Churg-Strauss syndrome, a systemic granulomatous and vasculitic process which also involves the lung, has been reported in an increasing number of patients receiving several drugs (glucocorticosteroids, leukotriene receptor antagonists, and macrolide antibiotics).<sup>112-114</sup> A causal relationship between these drugs and the Churg-Strauss syndrome has not been established. This life-threatening disease usually occurs in patients with a history of asthma, especially after oral glucocorticosteroid withdrawal.

**Immunologic hepatitis.** There is strong circumstantial evidence that immunologic hepatitis occurs after sensitization to para-amino-salicylic acid, sulfonamides, and phenothiazines.<sup>115</sup> Cholestatic jaundice is a prominent feature of phenothiazine-induced liver disease. Less well-defined are possible immunologic aberrations associated with hepatocellular changes occurring after halothane, anti-convulsives, erythromycin, indomethacin, and isoniazid.

**Blistering disorders: (1) Erythema multiforme minor.** Erythema multiforme minor appears to be a cell-mediated hypersensitivity reaction associated with viruses, other infectious agents, and drugs. It is often referred to as erythema multiforme "minor" and is manifested by pleomorphic cutaneous eruptions, at times bullous.<sup>116</sup> Target lesions are also characteristic. If a drug cause is suspected, the drug should be stopped immediately and the addition of glucocorticosteroids may be necessary. Antihistamines may help pruritus. Early treatment of erythema multiforme minor (prednisone 1 mg/kg/qd) may prevent progression to the more serious erythema multiforme major/Stevens-Johnson syndrome.

(2) *Erythema multiforme major/ Stevens-Johnson syndrome*. Drugs are an important cause of the erythema multiforme major/Stevens-Johnson syndrome (EMM/SJS) as well as toxic epidermal necrolysis (TEN). Thus far, more than a hundred drugs have been implicated as causes of these syndromes. In a large prospective cohort study, drugs associated with a high relative risk of developing SJS or TEN were sulfonamides, cephalosporins, imidazole agents, and oxycam derivatives; while drugs in the moderate risk category included quinolones, carbamazepine, phenytoin, valproic acid, and glucocorticosteroids.<sup>117</sup> As previously described under Physical Examination (see p 679), target and bullous lesions primarily involving the extremities and mucous membranes are characteristic of EMM while the features of SJS are confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than one mucosal surface, that are accompanied by high fever and severe constitutional symptoms. Ocular involvement may be particularly serious. Liver, kidney and lungs may be involved singly or in combination. As soon as the diagnosis is established, the suspected drug should be stopped immediately. The use of glucocorticosteroid therapy is controversial.<sup>117-119</sup> If it is started, it should probably be started early in the course of the disease and very large doses (eg, 80 to 160 mg) of intravenous methylprednisolone (every 4 to 6 hours) should be used. If this treatment is started too late in the course of the disease (ie, 3 to 4 days after onset), it is possible that TEN could supervene, in which case systemic glucocorticosteroids are contraindicated.<sup>116,120</sup>

(3) *Toxic epidermal necrolysis*. Stevens-Johnson syndrome and TEN are probably part of a single spectrum. If epidermal detachment is less than 10%, the disease is probably Stevens-Johnson but when epidermal detachment reaches 30% or more, the diagnosis of toxic epidermal necrolysis is probable.<sup>117</sup> In cases with detachment of 10% to 30% of the epidermis, the

two syndromes are overlapping. Toxic epidermal necrolysis is almost always drug-induced and is manifested by widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. Significant loss of skin equivalent to a third degree burn occurs. Glucocorticosteroids are contraindicated in this condition which must be managed in a burn unit.<sup>115,116</sup> There is a significant risk of infection and mortality is significant. Toxic epidermal necrolysis should be distinguished from the scalded skin syndrome, a disorder caused by staphylococcal bacterial toxin and characterized by the massive skin cleavage and separation in the uppermost epidermis. Recently, intravenous gamma globulin (0.2 to 0.75 g/kg body weight per day for 4 days) provided dramatic improvement with complete recovery in some TEN patients with increased levels of Fas ligand.<sup>121</sup>

**“Serum sickness-like reactions” associated with cephalosporins.** Cefaclor and cefprozil are associated with “serum-sickness-like” reactions characterized primarily by severe erythema multiforme and arthralgias. There is no evidence of an antibody-mediated basis for this reaction.<sup>122,123</sup> So far, this reaction has only been reported with these drugs. Anecdotally, affected patients later have tolerated non-related cephalosporins. Such patients should avoid the offending drugs and other cephalosporins with similar side chains. “Serum-sickness-like” reactions to cefaclor appear to result from altered metabolism of the parent drug resulting in reactive intermediate compounds.<sup>124</sup> This altered metabolism can often be documented in a parent of the patient.

## 2. Immunologic Nephropathy

The major example of drug-induced immunologic nephropathy is an interstitial nephritis induced by large doses of benzylpenicillin, methicillin, or sulfonamides. In addition to symptoms of tubular dysfunction, these patients demonstrate fever, rash, eosinophilia (especially in the urine), and high lev-

els of total IgE which revert to normal upon discontinuation of the offending drug.<sup>21</sup> The predominant lesion of the nephrotic syndrome induced by gold, penicillamine, and allopurinol is a membranous glomerulonephritis. An immunologic basis of this lesion is suggested by deposition of IgG, IgM, and C3 in glomerular lesions.<sup>49</sup> In the rare pulmonary-renal syndrome induced by penicillamine, “lumpy” intraglomerular deposits of complement and/or immunoglobulins are commonly observed.<sup>111</sup>

## 3. Cancer Chemotherapeutic Agents

Cancer chemotherapeutic agents are well recognized as causes of hypersensitivity reactions.<sup>125</sup> Some agents, such as L-asparaginase cause hypersensitivity reactions in more than 10% of patients when given intravenously.<sup>126</sup> The reaction rate is less when it is given by the intramuscular route. Immediate hypersensitivity Type 1 reactions are the most common. Doxorubicin, cisplatin, and carboplatin are drugs commonly associated with IgE-mediated Type 1 reactions.<sup>127,128</sup> The latter two drugs have been reported to cause anemia probably mediated by a cytotoxic immunologic reaction. In addition, some reactions due to these drugs or excipients in parenteral formulations appear to be mediated by non-immunologic degranulation of basophils and/or mast cells (eg, Cremophor-El, a lipid solvent vehicle in some intravenous preparations, particularly paclitaxel).<sup>13</sup> Bleomycin has been reported to cause arthralgias, pulmonary infiltrates and fever, presumably due to immune complexes.<sup>125,129</sup>

Methotrexate is the most frequent cause of non-cytotoxic pulmonary reactions.<sup>130,131</sup> Symptoms of fever, cough, and dyspnea may occur anywhere from several days to several months after initiation of therapy. The chest roentgenogram is characterized by a diffuse, fine interstitial infiltrate. When the drug is discontinued, symptoms and pulmonary infiltrates typically clear within a few days. If the drug is inadvertently continued, interstitial fibrosis may ensue. Bleomycin

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and procarbazine are most commonly associated with cytotoxic pulmonary reactions but also have been reported to cause reactions similar to those ascribed to methotrexate.<sup>110,130</sup>

#### 4. Blood and Blood Products

Acute urticarial reactions occur in 1% to 3% of blood transfusions, while significant bronchoconstriction/laryngeal edema and anaphylactic shock occur in 0.1% to 0.2% and 0.002% to 0.005%, respectively.<sup>132</sup> Diagnostic in vivo or in vitro tests are not available for such reactions. Rarely, a patient totally lacking serum IgA may develop specific IgE or IgG antibodies against IgA and subsequently react to IgA in the blood transfusion or in trace amounts contained in some preparations of intravenous gamma globulin.<sup>133,134</sup> Activation of complement and other non-IgE-mediated reactions may also occur after blood transfusions, presumably as a result of alloantigenic reactivity.<sup>132</sup> Reactions to human serum albumin are extremely rare (0.01%) but occasionally allergic patients exhibit positive prick tests to albumin-containing diluent solutions.<sup>135</sup> Such reactivity has been demonstrated in house dust mite-sensitive patients tested with mite culture medium containing human serum albumin components.

#### 5. Protamine

Protamine sulfate is a low molecular weight (4500 daltons) polycationic protein isolated from salmon testes. It is used to reverse the anti-coagulant effects of heparin after a variety of procedures including cardiopulmonary bypass and hemodialysis. It is also complexed to insulin [neutral protamine Hagedorn (NPH) insulin] in order to delay absorption. Immediate generalized reactions to protamine including hypotension, shock, and death have been reported.<sup>63,136,137</sup> The occurrence of dose-dependent hypotension after rapid intravenous administration may be a manifestation of non-specific histamine release.<sup>138</sup> The fact, however, that diabetic patients receiving protamine-containing insulins appear to be at 40 to 50 times greater risk for

developing anaphylaxis and other adverse reactions to intravenous protamine suggests that immune mechanisms are also involved.<sup>136</sup> Detailed information about these reactions and recommended management may be found in "Practice Parameters of the Diagnosis and Management of Anaphylaxis" (J Allergy Clin Immunol 1998;101:S507-S509).

#### 6. Heparin

Adverse reactions to heparin include localized urticarial reactions at injection sites, hypereosinophilia and anaphylaxis, all of which are immunologically mediated.<sup>64,139,140</sup> Heparin-induced thrombocytopenia may present in various forms. Mild thrombocytopenia is due to platelet aggregation and is reversible after stopping the drug.<sup>139</sup> A more severe clinical problem is sudden and massive thrombocytopenia, thrombosis, and necrosis which occurs after about 5 days of treatment. This is caused by immune complexes, a component of which is a heparin-dependent IgG specific for platelet factor 4.<sup>139,141</sup> This syndrome has not been observed in patients treated with low molecular weight heparin.<sup>142</sup> If this occurs, heparin should be discontinued and the use of warfarin or anti-platelet drugs should be considered.<sup>139</sup>

#### 7. Drug Reactions During the Operative and Perioperative Periods

Anaphylactic/anaphylactoid reactions are not infrequent during general anesthesia.<sup>143</sup> These reactions may be attributed to a number of drugs commonly used in an operative setting. These include induction agents, muscle relaxing agents, opiates, antibiotics, and contact with latex allergen. The incidence of life-threatening reactions to muscle relaxants has been estimated at 1 in 4,500 anesthesia events.<sup>144</sup> Some muscle relaxants, such as curare, are potent histamine releasing agents.<sup>145,146</sup> Others such as atracurium, pancuronium, and vecuronium are less potent in this regard. Drug-specific IgE antibodies have been demonstrated to some of these agents so that it is apparent that reactions to muscle relaxants may involve more than

one mechanism.<sup>147</sup> The diagnosis and management of reactions occurring during and after surgery are discussed in more detail in "Practice Parameters of the Diagnosis and Management of Anaphylaxis" (J Allergy Clin Immunol 1998;101:S512-S515).

#### 8. Local Anesthetics

Possible systemic allergy to local anesthetics is often of concern to patients and their dentists or physicians. Documentation of IgE-mediated reactions is rare. Most adverse reactions to local anesthetics are due to nonallergic reactions that include vasovagal reactions, toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine or anxiety.<sup>148</sup> Of these, anxiety is probably the most difficult to manage; therefore, the history of a previous reaction must be carefully evaluated. First, it is necessary to determine the type of local anesthetic to be used. Local anesthetics are either group 1 benzoic acid esters (eg, procaine and benzocaine) or group 2 amides (eg, lidocaine and mepivacaine). While the benzoic acid esters often cross-react with each other, they do not cross-react with the group 2 amide drugs. Graded challenge tests may then be performed using incremental concentrations of the local anesthetic which the dentist intends to use. This test reagent should not contain epinephrine or other additives such as parabens or bisulfites. When there is concern about a previously reported reaction, skin testing and incremental challenge with a non-cross-reacting drug (ie, from another class of local anesthetics) is a reasonable approach in the evaluation of a possible reaction.

A simple graded challenge procedure is used to demonstrate whether a reaction will occur.<sup>149</sup> *Prick skin tests are first performed with the undiluted anesthetic. If this is negative, successive injections (subcutaneous or intracutaneous) of 0.1 mL of 1:100 dilution, 1:10 dilution and the full strength solution are given at 15-minute intervals. If reactions are not encountered, 0.5 to 1 mL of the anesthetic is injected subcutaneously.* Using this protocol, there

have been no serious allergic reactions reported following administration of local anesthetics if the skin tests and test dosing are negative.<sup>150</sup>

Dentists and other health care professionals may develop contact dermatitis from local anesthetics. In the event that this occurs, patch testing should be performed to determine the degree of sensitization to the suspected local anesthetic and identify the agent(s) which is least likely to produce a reaction.

### VIII. PSEUDOALLERGIC REACTIONS

A group of reactions known as pseudoallergic must be differentiated from immune-mediated syndromes.<sup>151</sup> These are mediated by a diverse group of agents such as opiates, ASA/NSAIDs, colloid volume expanders, basic polypeptide agents (eg, polymixin B, ACTH) RCM, and excipients (eg, Cremophor-EL), among others. Acute reactions to these substances are caused by direct release of mediators from mast cells and basophils resulting in the classic end organ effects that these mediators exert. Direct mediator release occurs without evidence of a prior sensitization period, specific IgE antibodies, or antigen-antibody bridging on the mast cell/basophil cell membrane. The nonimmune reaction is immediate and often severe. Because it is nonimmunologic it may occur the first time that the host is exposed to these agents. The reactions are of further interest because they can also be elicited by small doses of the offending substance. It is possible that some of these reactions could be based in part upon nonimmunologic release of anaphylatoxins (C3a, C5a) through activation of the alternative complement pathway. Neuropeptides (eg, substance P) and endorphins may also activate and induce mediator release from mast cells. Osmotic alterations may lead to non-specific mediator release (eg, hyperosmolar mannitol) but such physical effects are more likely to occur at local tissue sites such as the nose or bronchi.

#### A. Opiates

Opiates such as morphine, meperidine, codeine, and narcotic analogs can stimulate mast cell-mediated release directly without an immunologic mechanism. Patients with this problem exhibit generalized pruritus and urticaria after injection of the respective narcotic. Occasional mild wheezing may be noted. Skin tests to opiates are difficult to interpret because these agents cause release of histamine from skin mast cells in all patients. Very dilute skin test concentrations have been recommended if an IgE-mediated reaction is suspected.<sup>152</sup> Some opiate reactions can be attenuated by preadministration of antihistamines. Narcotic-induced pseudoallergic reactions are rarely life-threatening. If there is a positive history of such a reaction to an agent and analgesia is required, a non-narcotic alternative pain medication should be selected. If this does not control pain, graded challenge with an alternative opiate up to a dose that will control pain should be tried. A single case of a documented IgE-mediated reaction to morphine has been reported.<sup>153</sup>

#### B. Radiocontrast Media

Radiocontrast media containing organic iodine may cause adverse reactions such as generalized urticaria/angioedema, bronchospasm, laryngospasm, shock, and death. A review of 10,000 consecutive intravenous urograms reveals that the incidence of pseudoallergic reactions is 1.7%.<sup>154</sup> The frequency of fatal reactions is 1 in 50,000 intravenous polygram procedures.<sup>155</sup> These adverse reactions are not mediated by specific IgE antibodies. Only 16% of individuals with a previous immediate generalized reaction after intravenous injection of iodinated radiographic compound respond with symptoms on the second challenge.<sup>156</sup> If these reactions had been mediated by specific IgE, it would be expected that a higher percentage of such patients would have experienced generalized reactions after the second challenge dose. No single pathogenic mechanism accounts for these unpredictable clinical manifestations but it is likely that mast cell activation accounts for the ma-

majority of these reactions. Activation of complement components has been described but not in all cases. Radiocontrast media can also cause intravascular volume expansion and precipitate "cardiogenic" pulmonary edema in patients with ischemic cardiac heart disease.<sup>157</sup> There is no evidence that sensitivity to seafood or "iodine" predisposes or is cross-reactive with RCM reactions. Although predictive tests are not available, patients with documented atopic profiles and those using beta blocking agents appear to be at significant risk for RCM anaphylactoid reactions.<sup>158,159</sup>

Management of a patient who requires RCM and has had a prior reaction to RCM includes the following (1) determine if the study is essential; (2) determine that the patient understands the risks; (3) ensure proper hydration; (4) use a non-ionic, lower osmolar RCM, especially in high risk patients (asthmatic patients, patients on beta blockers and those with cardiovascular disease)<sup>160</sup> and (5) use a pretreatment regimen which has been documented to be successful in preventing most reactions.<sup>161</sup> *One reported regimen consists of prednisone 50 mg (p.o.) 13, 7, and 1 hours before the procedure, diphenhydramine 50 mg one hour before the procedure and either ephedrine 25 mg or albuterol 4 mg 1 hour prior to the procedure. Some investigators prefer combining an H<sub>2</sub> antagonist with the H<sub>1</sub> antagonist one hour before the procedure and omitting ephedrine or albuterol.*

#### C. Other Agents

Anaphylactoid reactions have been described after administration of many colloid volume expanders (dextran, gelatin, hydroxyethyl starch, and human serum albumin).<sup>135</sup> An effective graded challenge protocol may be used to prevent severe anaphylactoid reactions to dextran contained in iron-dextran complexes.<sup>162</sup> This may be life saving in patients who require parenteral iron. Life threatening reactions to the osmotic diuretic, mannitol, is most likely due to hyperosmolar-dependent histamine release. Systemic anaphylactoid reactions may occur after par-

enteral administration of Cremophor-El, a solvent for paclitaxel, teniposide, cyclosporin, and some anesthetics. There are also anecdotal reports of reactions to sodium benzoate and chlorobutanol that are used as preservatives in various biologicals. Some drugs may have clinical presentations that often cannot be distinguished from anaphylaxis. These include ASA, NSAIDs, vancomycin, protamine, and quinolones.

## IX. NON-IMMUNE DRUG IDIOSYNCRASY/INTOLERANCE REACTIONS

### A. Aspirin and Non-Steroidal Anti-inflammatory Agents

Aspirin and NSAIDs cause a spectrum of adverse reactions which include (1) cardiorespiratory, anaphylactoid reactions occurring within minutes after ingestion of ASA or an NSAID; (2) urticaria and/or angioedema after ingestion of ASA/NSAID; (3) exacerbation of urticaria in patients with chronic idiopathic urticaria; or (4) asthma with or without rhinoconjunctivitis in about 10% of patients with chronic rhinitis, sinusitis, nasal polyps and/or asthma.<sup>163</sup> The association of asthma, nasal polyps, and aspirin sensitivity is termed the aspirin triad. *The nomenclature ascribed to this reaction is not standardized and terms such as aspirin idiosyncrasy, aspirin intolerance, aspirin sensitivity or simply, aspirin-induced asthma are commonly used.*<sup>164</sup> A few episodes of allergic alveolitis (hypersensitivity pneumonitis) have been reported after ingestion of an NSAID.<sup>165</sup>

*The role of IgE-mediated mechanisms in patients who experience acute urticaria/angioedema after ingestion of these drugs is controversial. Although several early studies reported anti-aspirin antibodies in some patients, they did not correlate either with urticarial or respiratory symptoms.*<sup>166,167</sup> Specific antibodies to aspirin anhydride, a former contaminant of commercial aspirin, were encountered in a few patients.<sup>168</sup> Anaphylactoid reactions to ASA and NSAIDs associated with vascular collapse are sugges-

tive of anaphylaxis because they occur after 2 or more exposures to ASA or to a specific NSAID and these patients do not have preexistent histories of urticaria, nasal polyps, and asthma.<sup>169</sup> These patients do not experience cross-reactions with other NSAIDs which inhibit COX-1 and COX-2 enzymes.<sup>164</sup>

The bronchoconstriction that occurs in asthmatics with nasal polyps is most likely due to aspirin-induced blockage of COX-1 and COX-2 specific cyclooxygenase metabolic pathways with subsequent decreased synthesis of PGE<sub>2</sub> which results in accumulation of 5-lipoxygenase and increased production of leukotrienes.<sup>164,169</sup> Agents that inhibit 5-lipoxygenase activity or leukotriene (LT) receptors may be beneficial in this syndrome.<sup>170,171</sup> All patients with the ASA triad and a third of patients with chronic idiopathic urticaria have cross-reactions with NSAIDs. Acetaminophen in doses >1000 mg and pyrazolones that have stronger blocking effects on the cyclooxygenase pathway induce cross-reactions in about a third of aspirin-sensitive patients. Baseline urinary leukotriene E<sub>4</sub> levels are increased in ASA-sensitive patients compared with ASA-tolerant asthmatics and increase markedly 2 to 4 hours after ASA challenge.

The diagnosis of ASA/NSAID intolerance can usually be established by history and often does not require confirmation. Skin testing is of no value and there are no commercially available in vitro tests for detection of ASA and NSAID sensitivity. When the history is unclear or erroneous (about 15% of the time) or where more definite diagnosis is required, the only acceptable diagnostic test is a controlled oral challenge test graded test dosing.<sup>163</sup> When the history is primarily urticaria or a respiratory reaction, test dosing may be performed in an outpatient setting with appropriate emergency equipment.<sup>172</sup>

Patients with intolerance reactions to ASA/NSAID are also at risk for developing similar reactions to other drugs or excipients. *Several earlier studies revealed that a small percent-*

*age of individuals with aspirin intolerance develop bronchospasm after challenge with tartrazine, a colorant additive structurally related to pyrazolones.*<sup>173-175</sup> *These results were not confirmed by other investigators whose patients were receiving bronchodilators in order to stabilize airways before placebo and tartrazine challenges.*<sup>176,177</sup> *The symptoms produced by tartrazine in these individuals are usually similar to those produced by aspirin and a similar pathogenetic mechanism(s) is postulated. Adverse reactions to tartrazine can occur in the absence of ASA/NSAID intolerance.*<sup>178</sup>

Management includes selection of analgesics with minimal or no inhibition of specific COX-1 cyclooxygenase activity [eg, acetaminophen (<1,000 mg), nonacetylated salicylates, opiates, and dextropropoxyphene]. It has yet to be determined whether COX-2 inhibitors will be safely tolerated by patients with ASA-induced asthma.<sup>164</sup> Desensitization of ASA-intolerant asthmatics may be appropriate if ASA or an NSAID is therapeutically necessary or asthma is poorly controlled with current medical management. Aspirin desensitization is not effective in aspirin-sensitive urticaria and/or angioedema.<sup>179</sup> Aspirin desensitization in patients with a history of ASA-induced systemic (anaphylactoid) reactions should be performed in an intensive care facility. It is not without risk but has been successful in selected patients.<sup>169</sup>

### B. Angiotensin-Converting Enzyme (ACE) Inhibitors

Two major adverse effects, cough and angioedema, are associated with the use of ACE inhibitors.<sup>180,181</sup> Generally cough and angioedema do not occur in the same patient. These symptoms are not associated with immunologic reactions. Although plasma bradykinin levels are elevated in many of these patients, the etiologic basis of bradykinin activation is not known.<sup>182</sup>

The incidence of cough may range up to 25% and about 10% of patients require discontinuation of therapy.<sup>180</sup>

Cough is twice as common in women than men. In most cases, cough disappears within 1 to 2 weeks after discontinuation of the respective drug. The incidence of cough associated with the use of enalapril and lisinopril is higher than that associated with the use of captopril.<sup>183</sup> Angiotensin II receptor inhibitors do not induce cough.

Angioedema is a potentially life-threatening complication of ACE inhibitors. It appears in 0.1% to 0.2% of patients receiving these drugs. The temporal relationship between initiation of these drugs and occurrence of angioedema is unpredictable and differs from the temporal pattern of other adverse drug reactions. In addition the pattern of relapses and remissions is atypical of drug allergy. The majority of reactions occur more than 1 month after the initial dose. About one-third of patients experiencing these episodes require hospitalization; 10% require intensive care.<sup>181</sup> These statistics increase considerably if recurrences occur (ie, hospitalization, 45% and intensive care, 28%). Further, intubation is more likely to be required in the treatment of relapsing patients; therefore, physician recognition of this syndrome is essential for prevention of relapses.<sup>181</sup> As is the case with ACE-induced cough, patients receiving enalapril and lisinopril are more likely to experience these reactions than those on captopril. There have been rare reports of abdominal pain and ascites associated with angioedema of the abdominal viscera due to ACE inhibitors. Angioedema may persist for several weeks after the drug is discontinued. There are several reports of angioedema associated with use of angiotensin II receptor inhibitors.<sup>184</sup>

### C. Preservatives

Some preservatives may evoke cough and bronchoconstriction in susceptible asthmatic patients after exposure to nebulizer solutions or formulations containing benzalkonium chloride or sulfites.<sup>185</sup> It has been suggested that susceptibility to sulfites in some asthmatic patients may be due to a deficiency of sulfite oxidase.<sup>186</sup>

## X. ADVERSE DRUG REACTIONS IN PATIENTS WITH HIV INFECTION/AIDS

Drug reactions are common in patients with AIDS and, in some cases the incidence of reactions may be related to the degree of immunodeficiency.<sup>187-197</sup> These reactions cause significant morbidity and mortality in this population. Unfortunately, the pathogenesis of these reactions is unknown. Adverse reactions to sulfonamides (SMDs) may complicate both treatment and prophylaxis of *Pneumocystis carinii* pneumonia in many patients with AIDS.<sup>187-195</sup> Unlike reactions to amoxicillin<sup>196</sup> and anti-mycobacterial agents,<sup>197</sup> adverse reactions to SMD may decline with HIV disease progression.<sup>198</sup> To date, risk factors for the development of drug intolerance/reactivity in patients with AIDS have not been clearly identified. Evidence exists to suggest that coexistent cytomegalovirus or Epstein-Barr virus infections, altered drug metabolism, slow acetylator phenotype, high-dose TMP-SMX treatment and/or glutathione deficiency may play a role in the development of reactivity.<sup>199-204</sup> Adverse cutaneous SMD reactions may be tolerated without ceasing therapy in some cases. Sulfonamides should be discontinued immediately however, if any of the following develop: (1) persistent rash and/or fever for more than 5 days; (2) absolute neutrophil count  $<500/m^3$ ; (3) hypotension; (4) dyspnea; or (5) any signs of blistering, desquamation of the skin or mucous membrane involvement.<sup>194</sup>

There appears to be a relationship between the development of adverse SMD reactions and the dose administered, since some patients can continue treatment after interruption of therapy or lowering of the dosage.<sup>188,196,198,200</sup> The degree of clinical cross-sensitivity between different SMDs is not known. The degree of clinical cross-sensitivity between TMP-SMX and dapsone is thought to be low, and it appears that the majority of patients who react to TMP-SMX may tolerate dapsone. Dapsone, however, probably should not be used in those patients in whom

TMP-SMX caused the Stevens-Johnson syndrome or visceral involvement such as hepatitis or pneumonitis.<sup>192</sup>

The most common reaction to SMDs is a morbilliform, maculopapular eruption often associated with fever that occurs after 7 to 12 days of therapy. Immediate (anaphylaxis, urticaria, and mucosal angioedema) and delayed (erythema multiforme minor, erythema multiforme major/Stevens-Johnson syndrome, toxic epidermal necrolysis) hepatic, hematologic, renal, and immune complex reactions may occur. The spectrum of clinical manifestations of SMD reactions in patients with AIDS suggests that most of these reactions are not IgE-mediated. In addition, the observation that desensitization protocols beginning with relatively high starting doses are often successful in SMD-allergic AIDS patients lends further support to the impression that an alternative pathogenic mechanism is operative. The possible increased prevalence of slow acetylation and altered activity of oxidative metabolic pathways in AIDS patients with acute illnesses may partly explain the increased incidence of adverse drug reactions in these patients.<sup>195,199,202</sup> Sulfonamide-specific IgG and IgM antibodies have been found in patients with AIDS, both those with and without skin reactions to SMDs. It is unlikely that these antibodies play a pathogenic role in SMD hypersensitivity reactions.<sup>205</sup> For those individuals who develop maculopapular rashes after SMD administration, several graded challenge protocols have been developed and used successfully.<sup>53,206-209</sup> Reintroduction of a SMD by one of these protocols optimally should not take place any earlier than 1 month following the initial adverse reaction nor should any of these be used in individuals with a history of bullous dermatitis or Stevens-Johnson syndrome. It may be started earlier, however, if treatment of a serious infection requiring these drugs is necessary. Sulfadiazine,<sup>210</sup> acyclovir,<sup>211</sup> zidovudine, dapsone, and pentamidine<sup>212</sup> "desensitization" protocols have also been developed for patients with AIDS. Ciprofloxacin-induced anaphylactoid re-

actions may occur more frequently in patients with AIDS.<sup>103,213</sup>

In addition to SMDs, patients with AIDS may have an increased frequency of adverse reactions to a number of other agents including (1) anti-tuberculous agents, (2) pentamidine, (3) amoxicillin-clavulanic acid, (4) clindamycin-primaquine, (5) carbamazepine, (6) phenytoin, (7) thalidomide, (8) foscarnet, and (9) zidovudine.<sup>195,214</sup> The fact that these reactions are clinically diverse suggests that they may be produced by a variety of mechanisms.

It is likely that the pathogenic mechanisms responsible for reactions to SMD in patients with AIDS are multifactorial. While these reactions are often described as "allergic" in nature, it is unlikely that a single mechanism alone is operative. In fact, there are data to support both toxic and immunologic mechanisms. In addition, other factors such as high-dose SMD therapy and severe immunodeficiency may influence the development of SMD hypersensitivity in patients with AIDS.<sup>191,200,215</sup>

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