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# Drug Allergy: An Updated Practice Parameter

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology.

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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing “Drug Allergy: An Updated Practice Parameter.” This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

**Reprint requests:** Joint Council of Allergy, Asthma & Immunology, 50 N. Brockway St, #3-3, Palatine, IL 60067.

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**PREFACE**

The objective of “Drug Allergy: An Updated Practice Parameter” is to improve the care of patients by providing the practicing physician with an evidence-based approach to the diagnosis and management of adverse drug reactions. This document was developed by a Working Group under the aegis of the Joint Task Force on Practice Parameters, which has published 26 practice parameters and updated parameters for the field of allergy/immunology (these can be found online at [www.jcaai.org](http://www.jcaai.org)). The 3 national allergy and immunology societies—the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI)—have given the Joint Task Force the responsibility for both creating new parameters and updating existing parameters. This parameter builds on “Disease Management of Drug Hypersensitivity: A Practice Parameter,” which was published in 1999 by the Joint Task Force on Practice Parameters. It follows the same general format as that document, with some substantive changes reflecting advancements in scientific knowledge and their effect on management of drug allergy. This document was written and reviewed by specialists in the field of allergy and immunology and was exclusively funded by the 3 allergy and immunology organizations noted above.

A Working Group chaired by Roland Solensky, MD, prepared the initial draft, which was then reviewed by the Joint Task Force. A comprehensive search of the medical literature was conducted using Ovid MEDLINE and the Cochrane Database and Keywords relating to drug allergy. Published clinical studies were rated by category of evidence and used to establish the strength of clinical recommendations. The working draft of “Drug Allergy: An Updated Practice Parameter” was reviewed by a large number of experts in allergy and immunology. These experts included reviewers appointed by the AAAAI and ACAAI. The authors carefully reviewed and considered additional comments from these reviewers. The revised final document presented here was approved by the sponsoring organizations and represents an evidence-based; broadly accepted consensus parameter.

This updated parameter contains several significant changes from the original parameter on “Disease Management of Drug Hypersensitivity: A Practice Parameter.” The title of the parameter was changed from drug hypersensitivity to drug allergy. In this updated parameter the term *drug*

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*allergy* is defined as an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person. The implication is that drug allergy does not simply include only IgE-mediated reactions. Another significant change is the introduction of the new term *induction of drug tolerance* to encompass classic IgE-mediated drug desensitizations and other non-IgE-mediated “desensitization” procedures for various medications. In addition, several new sections have been added, including a new glossary with new terms, new classifications and subclassifications for drug reactions, and new sections on drug allergic reactions to chemotherapeutic agents, corticosteroids, disease-modifying antirheumatic drugs, antimycobacterial drugs, biologic modifiers, immunosuppressive agents, immunomodulatory agents, complementary medications, and drug-induced granuloma with or without vasculitis. Significant updates to sections on cutaneous manifestations of drug reactions, laboratory testing,  $\beta$ -lactam allergy, cross-reactivity between carbapenems and penicillin, and human immunodeficiency virus medications have been added. Finally, a number of protocols for induction of drug tolerance procedures have been added.

The Executive Summary emphasizes the key updates since the 1999 drug hypersensitivity parameter. This Executive Summary has been significantly expanded to include the new sections and highlight the major updates to this parameter. It should be noted that the Executive Summary does not discuss all of this parameter’s topics in depth. An annotated algorithm in this document summarizes the major decision points for the evaluation and treatment of patients who have experienced possible adverse drug reactions (Fig 1). This is followed by a list of summary statements that represent the key points to consider in the evaluation and management of drug hypersensitivity reactions. Within the evidence-based commentary, the summary statements are repeated and are followed by the text that supports that summary statement. The evidence-based commentary first discusses general issues relating to drug allergy, including definitions, classifications, risk factors, and the general approach to evaluation, diagnosis, management, and prevention (sections I through VI). Subsequently, specific types of drugs are discussed (section VII).

The Joint Task Force on Practice Parameters would like to thank the AAAAI, ACAAI, and JCAAI, who supported the preparation of the updated parameter, and the large number of individuals who have so kindly dedicated their time and effort to the preparation and review of this document.

## GLOSSARY

- *Adverse drug reactions* include all unintended pharmacologic effects of a drug except therapeutic failures, intentional overdosage, abuse of the drug, or errors in administration. They can be classified as predictable or unpredictable. Unpredictable reactions are further subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions.
- *Drug allergy* is an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person.
- *Anaphylaxis* is an immediate systemic reaction that occurs when a previously sensitized individual is reexposed to an allergen. It is caused by rapid IgE-mediated immune release of vasoactive mediators from tissue mast cells and peripheral basophils with a potential late component.
- *Pseudoallergic (anaphylactoid) reactions* are immediate systemic reactions that mimic anaphylaxis but are caused by non-IgE-mediated release of mediators from mast cells and basophils.
- *Drug intolerance* is an undesirable pharmacologic effect that may occur at low or usual doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. Humoral or cellular immune mechanisms are not thought to be involved, and a scientific explanation for such exaggerated responses has not been established (eg, aspirin-induced tinnitus at low doses).
- *Drug idiosyncrasy* is an abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug and has an unknown mechanism. It is not mediated by a humoral or cellular immune response but is reproducible on readministration. It may be due to underlying abnormalities of metabolism, excretion, or bioavailability (eg, quinidine-induced drug fever).
- *Aspirin-exacerbated respiratory disease (AERD)* is a clinical entity characterized by aspirin- or nonsteroidal anti-inflammatory–induced respiratory reactions in patients with underlying asthma and/or rhinitis or sinusitis. AERD does not fit precisely into a specific category of adverse drug reactions.
- *Drug tolerance* is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state of tolerance or that the mechanism involved was immunologic tolerance.
- *Induction of drug tolerance*, which has often been referred to as drug desensitization, is more appropriately described as a temporary induction of drug tolerance. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms. All procedures to induce drug tolerance involve administration of incremental doses of the drug. See Table 1 for characteristics of these 4 types of drug tolerance.
- *Drug desensitization* is one form of induction of immune drug tolerance (see above) by which effector cells are rendered less reactive or nonreactive to IgE-mediated immune responses by rapid administration of incremental doses of an allergenic substance.
- *Graded challenge* or test dosing describes administration of progressively increasing doses of a medication until a full dose is reached. The intention of a graded challenge is to verify that a patient will not experience an immediate

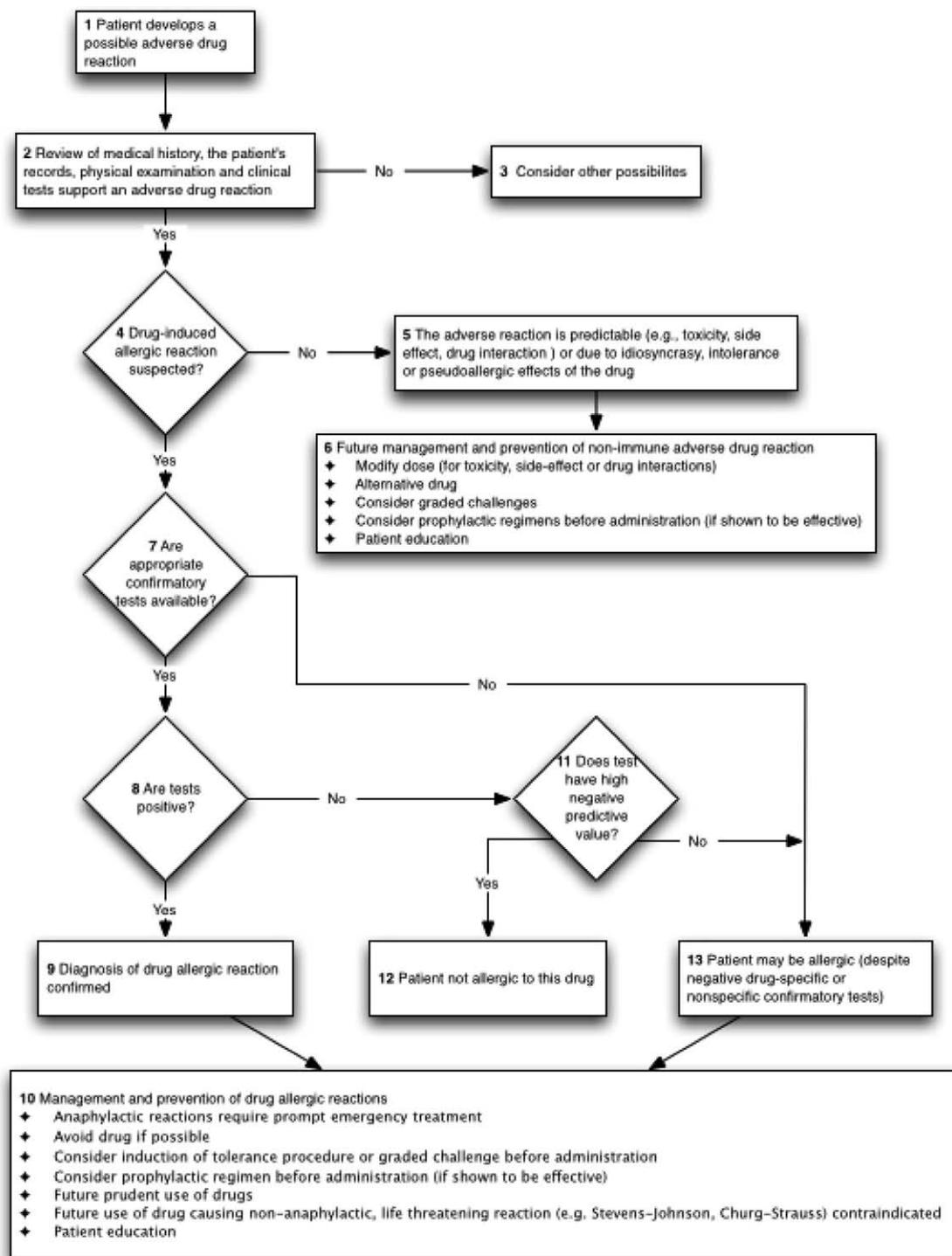


Figure 1. Algorithm for disease management of drug allergy.

Table 1. Classification of Induction of Drug Tolerance (Formerly Referred to as Desensitization)<sup>a</sup>

Type of drug tolerance	Time/duration	Initial dose	Possible outcomes	Example
Immunologic IgE (drug desensitization)	Hours	Micrograms	Antigen-specific mediator depletion, downregulation of receptors	Penicillin
Immunologic non-IgE	Hours to days	Milligrams	Unknown	Trimethoprim-sulfamethoxazole
Pharmacologic	Hours to days	Milligrams	Metabolic shift, internalization of receptors	Aspirin
Undefined	Days to Weeks	Micrograms to milligrams	Unknown	Allopurinol

<sup>a</sup> What has often been referred to as drug desensitization is more appropriately described as induction of drug tolerance. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and mixed or unknown mechanisms. All involved administration of incremental doses of the drug. This table indicates the characteristics of these 4 types of drug tolerance.

adverse reaction to a given drug. The medication is introduced in a controlled manner to a patient who has a low likelihood of reacting to it. Unlike procedures that induce drug tolerance, graded challenges usually involve fewer doses, are of shorter duration, and are not intended to induce drug tolerance.

- *The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome* is a drug-induced, multiorgan inflammatory response that may be life threatening. First described in conjunction with anticonvulsant drug use, it has since been ascribed to a variety of drugs.

## EXECUTIVE SUMMARY

### Classification of Adverse Reactions to Drugs

Adverse drug reactions (ADRs) result in major health problems in the United States in both the inpatient and outpatient settings. ADRs are broadly categorized into predictable (type A) and unpredictable (type B) reactions. Predictable reactions are usually dose dependent, are related to the known pharmacologic actions of the drug, and occur in otherwise healthy individuals. They are estimated to comprise approximately 80% of all ADRs. Unpredictable reactions are generally dose independent, are unrelated to the pharmacologic actions of the drug, and occur only in susceptible individuals. Unpredictable reactions are subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions. Both type A and type B reactions may be influenced by genetic predisposition of the patient.

In this parameter, drug allergy is defined as an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person. The classification of drug allergies is impeded by our limited understanding of the underlying mechanisms. Although the Gell-Coombs classification served a useful purpose in its time, it does not account for many common clinical problems. Nevertheless, when applicable we will still refer to recent modifications of that system. Our knowledge of IgE-mediated drug allergy is derived chiefly from the vast amount of research involving penicillin allergy. Beyond this, our knowledge of drug allergy mechanisms is limited but emerging.

There have, however, been great strides made in our understanding of other drug allergies and adverse drug reactions such as aspirin-exacerbated respiratory disease (AERD).

Drug allergy may be classified by the Gell-Coombs classification of human hypersensitivity: IgE-mediated (type I), cytotoxic (type II), immune complex (type III), and cellular mediated (type IV). Delayed hypersensitivity type IV reactions are mediated by cellular immune mechanisms. A recently proposed modification subdivides type IV reactions into 4 categories involving activation and recruitment of monocytes (IVa), eosinophils (IVb), CD4<sup>+</sup> or CD8<sup>+</sup> T cells (IVc), and neutrophils (IVd).<sup>1</sup> The classic reaction in this category is contact dermatitis, a condition in which the topical induction and elicitation of sensitization by a drug is entirely limited to the skin. It appears that Gell-Coombs type IV reactions are also responsible for delayed cutaneous eruptions, such as maculopapular exanthems due to antibiotics (eg, amoxicillin and sulfonamides) and acute generalized exanthematous pustulosis. Drug allergy may also be classified by the predominant tissue or organ involved (eg, systemic, cutaneous, hepatic), which is useful in light of the difficulty that sometimes occurs in determining the immunologic mechanism involved. Table 2 highlights the spectrum of drug allergic reactions and syndromes that will be discussed in greater detail in this parameter.

The p-i concept (pharmacologic interaction with immune receptors) is a recently proposed addition to drug hypersensitivity classification. In this scheme, a drug binds noncovalently to a T-cell receptor, which may lead to an immune response via interaction with a major histocompatibility receptor. In this scenario, no sensitization is required because there is direct stimulation of memory and effector T cells, analogous to the concept of superantigens.<sup>2,3</sup>

The structural characteristics of certain drugs, such as penicillin and peptides, may help predict the type of hypersensitivity reaction; however, this is not always the case. 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, sex, atopy, specific genetic polymorphisms, and inherent

Table 2. Drug Allergic Reactions and Syndromes

	Clinical manifestations	Examples of causative agents
IgE mediated	Urticaria, angioedema, bronchospasm, anaphylaxis	$\beta$ -Lactam antibiotics, platinum-based chemotherapeutics, perioperative agents
Cytotoxic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Immune complex	Serum sickness	Penicillin, infliximab, thymoglobulin
Delayed type hypersensitivity	Contact dermatitis, exanthems	Neomycin, glucocorticoids, penicillin, sulfonamide antibiotics
Hypersensitivity vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil
DRESS	Cutaneous, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Pulmonary drug hypersensitivity	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Systemic drug-induced lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Cutaneous drug-induced lupus erythematosus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium channel blockers, ACE inhibitors
Drug-induced granulomatous disease	Churg-Strauss syndrome, Wegener's granulomatosis	Propylthiouracil, leukotriene modifiers
Immunologic hepatitis	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Blistering disorders	Erythema multiforme, SJS, TEN	Sulfonamides, cephalosporins, imidazole anticonvulsants, NSAIDs
Serum sickness–like reactions	Erythema multiforme, arthralgias	Cefaclor, cefprozil
Immunologic nephropathy	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol

Abbreviations: ACE, angiotensin-converting enzyme; DRESS, drug rash with eosinophilia and systemic symptoms; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

predisposition to react to multiple unrelated drugs (multiple drug allergy syndrome).

### History and Physical Examination

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 and allergenicity of previously and 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. Cutaneous manifestations are the most common presentation for drug allergic reactions. Although drug allergic reactions may present with noncutaneous physical findings, these findings are generally nonspecific and are not nearly as helpful in diagnosis and management decisions. Therefore, the emphasis in this parameter on the physical examination focuses on cutaneous findings.

Characterization of cutaneous lesions is important in regard to determining the cause, further diagnostic tests, and management decisions. Numerous cutaneous reaction patterns have been reported in drug allergy, including exanthems, urticaria, angioedema, acne, bullous eruptions, fixed drug eruptions, erythema multiforme, lupus erythematosus, photosensitivity, psoriasis, purpura, vasculitis, pruritus, and

life-threatening cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), exfoliative dermatitis, and drug rash with eosinophilia and systemic symptoms (DRESS).<sup>4</sup>

### Diagnostic Tests

Possible clinical tests might include but are not limited to a chest x-ray examination, a complete blood cell count with differential, sedimentation rate, nuclear and cytoplasmic autoantibody tests, and other specific immunologic tests. A retrospective diagnosis of anaphylaxis may be determined by detecting an increase in serum total tryptase levels above baseline or in serum mature tryptase (also known as  $\beta$ -tryptase). 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. Relatively few studies with small numbers of patients have evaluated the specificity and sensitivity of third-generation assays for detection of penicillin specific IgE in vitro.<sup>5,6</sup> These studies demonstrate relatively high specificity (97%-100%) but lower sensitivity (29%-68%) for penicillin specific IgE. Therefore, although a positive in vitro test result for penicillin specific IgE is highly predictive of penicillin allergy, a negative in vitro test result does not adequately exclude penicillin allergy. The basophil activation test is a recently described method of evaluating expression of CD63

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on basophils after stimulation with an allergen.<sup>7</sup> There are limited data using this method to evaluate patients with possible allergies to  $\beta$ -lactam antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>8-10</sup> Further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool.

Patch testing is the most reliable technique for diagnosis of contact dermatitis caused by topically applied drugs. The diagnosis of contact dermatitis usually can be verified by patch testing. In recent years there have been reports concerning the diagnostic utility of patch tests with systemically administered drugs in non-IgE-mediated cutaneous drug reactions.<sup>11</sup> Drug patch testing may be useful for certain types of cutaneous drug reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions,<sup>12-14</sup> but generally is not helpful for SJS or urticarial eruptions.<sup>12-15</sup>

In complex cases where multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy may be useful in suggesting a drug-induced eruption. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy may not definitively exclude alternative causes.<sup>16</sup>

### Induction of Drug Tolerance and Graded Challenges

What has often been referred to as drug desensitization is more appropriately described in this parameter as a temporary induction of drug tolerance. Drug tolerance is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state of tolerance or that the mechanism involved was immunologic tolerance. Induction of drug tolerance procedures modify a patient's response to a drug to temporarily allow treatment with it safely. They are indicated only in situations where an alternate non-cross-reacting medication cannot be used. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms (Table 1). All procedures to induce drug tolerance involve administration of incremental doses of the drug. Through various mechanisms, these procedures induce a temporary state of tolerance to the drug, which is maintained only as long as the patient continues to take the specific drug.

Where there is a definite medical indication for the agent in question, either induction of drug tolerance or graded challenge procedures may be considered, depending on the history of the previous reaction and the likelihood that the patient is currently allergic to that agent. If there is a low likelihood of drug allergy, a graded challenge or test dose to the specific drug in question may provide a useful confirmation that administration of the drug will not result in an immediate reaction. The purpose of graded challenge is to cautiously administer a drug to a patient who is unlikely to be allergic to it and there is no intention to induce tolerance to the drug. Patients who tolerate a graded challenge are considered to not be allergic to the drug and are not at in-

creased risk for future reactions compared with the general population.

The choice of whether to introduce a clinically indicated drug via graded challenge or via induction of drug tolerance mainly depends on the likelihood that the patient is allergic at the time of the procedure. Patients who, based on their history and/or diagnostic test results, are unlikely to be allergic to a drug may undergo graded challenge. Patients who have a relatively higher likelihood of being allergic to a drug should undergo an induction of drug tolerance procedure. Graded challenge (or induction of drug tolerance) should almost never be performed if the reaction history is consistent with a severe non-IgE-mediated reaction, such as SJS, TEN, interstitial nephritis, hepatitis, or hemolytic anemia.

### Other Immunologic Drug Allergy Syndromes

Specific drugs or classes of drugs may be associated with characteristic syndromes, which may not conform to typical presentations defined by the Gell-Coombs classification system. Table 2 lists the various other immunologic drug allergic syndromes discussed in the parameter.

### Specific Drugs and Biologic Agents

Drug allergic reactions have been reported to most all medications. However, certain drugs are more frequently associated with specific types of reactions. Significant updates on the following drugs and biologic agents have been made in this updated parameter and are discussed elsewhere in more detail.

### Antimicrobials

The most important causes of immediate hypersensitivity reactions are antibiotics, particularly  $\beta$ -lactam antibiotics. Approximately 10% of patients report a history of penicillin allergy. However, up to 90% of these individuals are able to tolerate penicillin and are designated as having "penicillin allergy" unnecessarily.<sup>17,18</sup> Use of broad-spectrum antibiotics in patients designated as being "penicillin allergic" is associated with higher costs, increased antibiotic resistance, and may compromise optimal medical care.<sup>19</sup> Penicillin skin testing is the most reliable method for evaluating IgE-mediated penicillin allergy. Ideally, both major and minor determinant reagents are used for skin testing. Penicillin challenges of individuals skin test negative to penicilloylpolylysine and penicillin G<sup>20,21</sup> have similar reaction rates compared with individuals skin test negative to the full set of major and minor penicillin determinants.<sup>17,18</sup>

Varying degrees of allergic cross-reactivity between penicillin and cephalosporins have been documented. Overall, most patients with a history of penicillin allergy tolerate cephalosporins,<sup>22</sup> but there are rare reports of anaphylactic reactions, including fatal reactions.<sup>23</sup> Patients with a history of penicillin allergy who have negative skin test results to penicillin using major and minor determinants may receive cephalosporins safely.<sup>24</sup> Skin testing for cephalosporins and other  $\beta$ -lactam antibiotics is not standardized, as it is for

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penicillin. There is no allergic cross-reactivity between penicillin and monobactams. The degree of cross-reactivity between penicillin and carbapenems appears to be low.<sup>25,26</sup> IgE-mediated reactions to non- $\beta$ -lactam antibiotics may occur but are less common. There is no standardized skin testing for evaluation of immediate-type allergy to non- $\beta$ -lactam antibiotics.

Sulfonamide antibiotics rarely cause IgE-mediated reactions and more commonly result in delayed maculopapular exanthems, particularly in human immunodeficiency virus (HIV)-positive patients. There is no evidence to suggest allergic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides.<sup>27</sup> Vancomycin rarely causes IgE-mediated reactions, but more than 50% of patients experience immediate cutaneous erythema, flushing, and pruritus (red man syndrome), which is the result of non-IgE-mediated histamine release. Red man syndrome reactions can be prevented by slowing the rate of infusion and premedicating with histamine<sub>1</sub> receptor antihistamines. Although aminoglycosides rarely cause hypersensitivity reactions, there are individual case reports of IgE-mediated systemic reactions. Reports of IgE-mediated anaphylactic reactions to quinolones appear to be increasing, possibly due to increased use of these agents.<sup>28-31</sup> In vitro studies suggest a large extent of allergic cross-reactivity among quinolones,<sup>2,28</sup> but there are no clinical studies to confirm this. Delayed cutaneous eruptions appear in approximately 2% of quinolone-treated patients.<sup>32,33</sup> There is evidence to show that drug-specific T cells are responsible for delayed maculopapular exanthems from quinolones.<sup>2</sup>

Allergic drug reactions to antimycobacterial drugs can induce both minor and life-threatening reactions. Many allergic reactions were also encountered after use of second-generation drugs, including isoniazid, ethambutol, pyrazinamide, and rifampicin.<sup>34</sup> These include anaphylaxis, angioedema, pulmonary infiltrates, and cutaneous reactions.<sup>35-39</sup>

### Insulin and Oral Antidiabetic Drugs

Since the introduction of purified human recombinant insulin, allergy to insulin is rare and is now encountered in less than 1% of patients.<sup>40-43</sup> However, life-threatening allergic reactions to human insulin and insulin analogs (Aspart, Lispro, and Glargine) have been documented and can be confirmed by appropriate intracutaneous and/or in vitro testing.<sup>44,45</sup> The mechanisms of immunogenic reactions to recombinant human insulin are not entirely clear but may relate to structural changes of insulin, including insulin aggregation (fibrillation).<sup>46</sup> Leukocytoclastic vasculitis, generalized arteritis, granulomatous hepatitis, and autoimmune pemphigus vulgaris are rare immune-mediated reactions that have been described to occur during treatment with metformin and/or sulfonylurea antidiabetic agents.<sup>47-53</sup>

### Cancer Chemotherapeutic Agents

Hypersensitivity reactions have been reported for virtually all commonly used chemotherapeutic agents. Reactions range from mild cutaneous eruptions to fatal anaphylaxis. Some

reactions may be the result of excipients rather than the active drug, such as Cremophor-EL, a lipid solvent vehicle used in paclitaxel and other intravenous chemotherapeutics. In the taxane family, paclitaxel and docetaxel produce anaphylactic reactions in as many as 42% of patients on first administration,<sup>54</sup> suggesting an anaphylactoid mechanism. Pretreatment with systemic corticosteroids and antihistamines prevents the reaction in more than 90% of patients.<sup>55</sup> Patients who react despite pretreatment can usually be successfully desensitized.<sup>56-58</sup> Another option for patients who react to paclitaxel is to switch to docetaxel because most are able to tolerate it.<sup>59</sup> Platinum compounds (cisplatin, carboplatin, and oxaliplatin) typically cause hypersensitivity reactions after completion of several treatment courses,<sup>60,61</sup> suggesting an immunologic mechanism. Pretreatment with corticosteroids and antihistamines does not prevent these reactions.<sup>62</sup> Skin testing with the undiluted drug has been found to identify patients at risk of reactions, and skin testing should be repeated before each subsequent course with the drug.<sup>61,63,64</sup> For patients with positive skin test results, various rapid induction of drug tolerance protocols have been reported, but they are not uniformly successful.<sup>61,63,64</sup> Recently, a 12-step desensitization protocol for a variety of chemotherapeutic agents, including platinum compounds, has been reported to be completely successful in 413 procedures, with 94% of procedures having only a mild or no reaction.<sup>58</sup>

Methotrexate is a cause of noncytotoxic pulmonary reactions.<sup>65,66</sup> Methotrexate pneumonitis occurs most frequently within the first year of treatment, and the reported incidence of this reaction varies from 0.86% to 6.9%.<sup>67,68</sup> If use of the drug is inadvertently continued, interstitial fibrosis may ensue.

### Medications for Patients With HIV Infections and AIDS

Drug reactions are common in patients infected with the HIV virus, and in some cases, the incidence of reactions may be related to the degree of immunodeficiency.<sup>69-73</sup> Adverse reactions to sulfonamides may complicate both treatment and prophylaxis of *Pneumocystis jiroveci* pneumonia in many patients with AIDS. The most common reaction to sulfonamides is a morbilliform, maculopapular eruption often associated with fever that occurs after 7 to 12 days of therapy. For HIV-positive individuals who develop typical delayed maculopapular rashes after trimethoprim and sulfamethoxazole administration, many different induction of drug tolerance protocols have been developed and used successfully.<sup>74-85</sup> It is not clear how or to what extent the immune response to trimethoprim-sulfamethoxazole is modified during these types of induction of drug tolerance procedures. In a randomized trial of trimethoprim-sulfamethoxazole induction of drug tolerance vs rechallenge (single dose), the success rates were 79% and 72%, respectively, and the difference was not statistically significant.<sup>83</sup> Sulfadiazine, acyclovir, zidovudine, dapsone, and pentamidine induction of drug tolerance protocols have also been developed for patients with AIDS.<sup>86-91</sup>

At least 20 antiretroviral drugs are approved by the US Food and Drug Administration for highly active antiretroviral

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therapy of HIV-infected patients.<sup>92,93</sup> Many of these drugs have been associated with hypersensitivity responses ranging from mild cutaneous rashes to life-threatening SJS and TEN.<sup>94</sup> Abacavir, a nucleoside-analogue reverse transcriptase inhibitor, causes severe hypersensitivity in 4% to 5% of patients.<sup>95,96</sup> Such reactions have been identified with a genetic risk factor, the presence of HLA B 5701.<sup>97,98</sup>

### Medications for Autoimmune Diseases

A variety of allergic reactions to disease-modifying antirheumatic drugs (DMARDs) may occur, including gold salts, D-penicillamine, sulfasalazine, hydroxychloroquine, and leflunomide. Reactions such as vasculitis, DRESS, photodermatitis, and TEN have been reported with DMARDs. Newer immunomodulator agents have been introduced for several autoimmune diseases. Although hypersensitivity reactions to several of these have already occurred, it is too early to assess the global impact of adverse events for diverse immunologic interventions in early development. Allergic reactions to immunosuppressant and anti-inflammatory drugs may be encountered in the treatment of chronic cutaneous diseases. Dermatologic immunosuppressant drugs, such as macrolides (eg, cyclosporine, tacrolimus, pimecrolimus, and sirolimus), dapsone, and mycophenolate mofetil, have been reported to cause drug allergic reactions in addition to their known predictable adverse reactions.

### Perioperative Agents and Blood Products

Anaphylactic and anaphylactoid reactions during general anesthesia may be due to induction agents, neuromuscular blocking agents, antibiotics, opiates, and latex. Because anaphylactic reactions cannot be distinguished from anaphylactoid, nonimmune occurrences, it has been recommended that plasma histamine, tryptase, and specific IgEs (if available) may be ordered at the time of reaction and skin tests be performed later.<sup>99</sup> Immediate generalized reactions to protamine, including hypotension, shock, and death, have been reported.<sup>100,101</sup> Diabetic patients receiving protamine-containing insulins appear to be at 40 to 50 times greater risk for developing anaphylaxis.<sup>102,103</sup> Reactions due to blood and blood products include urticaria, anaphylaxis (particularly in patients with complete IgA deficiency), anaphylactoid reactions, and transfusion-related acute lung injury (TRALI). TRALI is a complex syndrome that has multiorgan manifestations and has only recently been identified to be an important cause of transfusion-associated morbidity and mortality.<sup>104,105</sup>

### Opiates

Opiates and their analogs are a common cause of pseudoallergic reactions that are generally mild, are not life-threatening, and can be attenuated by preadministration of histamine<sub>1</sub> receptor antihistamines. Skin test results to opiates are difficult to interpret because these agents cause release of histamine from skin mast cells in all patients.

### Corticosteroids

Allergic contact dermatitis due to topical application of corticosteroids is the most common type of allergic reaction induced by this class of drugs. Very rarely, immediate-type allergic reactions to corticosteroids have been described. Most such reported reactions are due to intravenous administration of methylprednisolone and hydrocortisone<sup>106-111</sup>; however, preservatives and diluents have also been implicated.

### Heparin

Hypersensitivity reactions to unfractionated heparin and low-molecular-weight heparin are uncommon and include thrombocytopenia, various cutaneous eruptions, hypereosinophilia, and anaphylaxis. Mild thrombocytopenia is due to platelet aggregation and occurs in 1% to 3% of patients treated with unfractionated heparin. Severe thrombocytopenia is caused by immune complexes, a component of which is heparin-dependent IgG specific for platelet factor 4.<sup>112</sup> This reaction usually occurs after approximately 5 days of treatment with unfractionated heparin and is associated with development of thrombosis and necrosis. A recent outbreak of anaphylactic reactions to heparin in the United States and Germany was attributed to a contaminant in heparin lots, an oversulfated form of chondroitin sulfate. This oversulfated chondroitin sulfate contaminant has been shown in vitro and in vivo to cause activation of the kinin-kallikrein pathway with generation of bradykinin, a potent vasoactive mediator, and C3a and C5a anaphylatoxins.<sup>113</sup> Clinically, reactions to contaminated heparin products were associated with hypotension and abdominal pain, and variably angioedema, but typically lacked urticaria and pruritus.<sup>114</sup> The findings of abdominal pain and angioedema are somewhat analogous to C1 inhibitor deficiency in which symptoms are due to local production of bradykinin.

### Local Anesthetics

Most adverse reactions to local anesthetics are not due to IgE-mediated mechanisms but are due to nonallergic factors that include vasovagal responses, anxiety, toxic reactions including dysrhythmias, and toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine effects. Documentation of IgE-mediated reactions is extremely rare.<sup>115-118</sup> When there is concern about a previously reported reaction, skin testing and incremental challenge with a local anesthetic is a reasonable approach in the evaluation of a possible reaction.

### Radiocontrast Media

Anaphylactoid reactions occur in approximately 1% to 3% of patients who receive ionic radiocontrast media (RCM) and less than 0.5% of patients who receive nonionic agents.<sup>119,120</sup> Severe life-threatening reactions are less common, occurring in 0.22% of patients receiving ionic RCM and 0.04% of patients receiving nonionic agents.<sup>121</sup> Risk factors for anaphylactoid reactions to RCM include female sex, asthma, and

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a history of previous anaphylactoid reaction to RCM;  $\beta$ -blocker exposure and/or the presence of cardiovascular conditions is associated with greater risk for more serious anaphylactoid reaction.<sup>122-126</sup> There is no convincing evidence in the medical literature that individuals with “seafood allergy” are at elevated risk for anaphylactoid reaction to RCM compared with the general population. Management of a patient who requires RCM and has had a prior anaphylactoid reaction to RCM includes the following: (1) determine whether the study is essential; (2) determine that the patient understands the risks; (3) ensure proper hydration; (4) use a nonionic, iso-osmolar RCM, especially in high-risk patients (asthmatic patients, patients taking  $\beta$ -blockers and those with cardiovascular disease); and (5) use a pretreatment regimen that has been documented to be successful in preventing most reactions.<sup>127-130</sup> Delayed reactions to RCM, defined as those occurring between 1 hour and 1 week after administration, occur in approximately 2% of patients.<sup>131</sup> These reactions most commonly manifest as mild, self-limited cutaneous eruptions and do not require any treatment.<sup>131</sup> The mechanism of delayed skin reactions to RCM appears to be T cell mediated.<sup>132</sup>

### Aspirin, NSAIDs, and Platelet Inhibitors

Aspirin and NSAIDs can cause a spectrum of drug allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis. AERD is a clinical entity characterized by aspirin- and NSAID-induced respiratory reactions in patients with chronic rhinosinusitis and asthma. AERD does not fit precisely into a specific category of adverse drug reactions. The mechanism of AERD is related to aberrant arachidonic acid metabolism. Patients with AERD also have increased respiratory tract expression of the cysteinyl leukotriene 1 receptor and heightened responsiveness to inhaled leukotriene E<sub>4</sub>.<sup>133,134</sup> Administration of aspirin leads to inhibition of cyclooxygenase 1 (COX-1) with resultant decrease in prostaglandin E<sub>2</sub>. Prostaglandin E<sub>2</sub> normally inhibits 5-lipoxygenase, but with a loss of this modifying effect, arachidonic acid molecules are preferentially metabolized in the 5-lipoxygenase pathway, resulting in increased production of cysteinyl leukotrienes. NSAIDs that preferentially inhibit COX-2 but also inhibit COX-1 at higher doses may result in reactions, depending on the dose given. Selective COX-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely.<sup>135-139</sup>

When patients with a history suggestive of AERD (ie, asthma, rhinosinusitis, and history of respiratory reaction to aspirin or aspirin-like drug) are challenged with aspirin, approximately 85% will have a respiratory reaction confirming the diagnosis.<sup>140</sup> A recent study showed that 100% of patients with a history of aspirin causing a severe reaction (poor response to albuterol with need for medical intervention) had positive oral aspirin challenges.<sup>141</sup> Management of patients with AERD involves avoidance of aspirin and NSAIDs and aggressive medical and/or surgical treatment of underlying

asthma and rhinitis/sinusitis. A pharmacologic induction of drug tolerance procedure (also known as aspirin desensitization), during which tolerance to aspirin can be induced and maintained, is an important therapeutic option for patients with AERD.

A second clinical presentation of aspirin and NSAID drug allergic reactions is an exacerbation of urticaria or angioedema in patients with chronic idiopathic urticaria. All drugs that inhibit COX-1 cross-react to cause this reaction. Selective COX-2 inhibitors are generally well tolerated in patients with chronic idiopathic urticaria, although there may be rare exceptions.<sup>142-144</sup> A third type of drug allergic reaction is aspirin or single NSAID-induced urticaria or angioedema or anaphylactic reaction, in which case other NSAIDs are tolerated.<sup>145-148</sup> A fourth type of drug allergic reaction to aspirin and NSAIDs is urticaria or angioedema due to aspirin and any NSAID that inhibits COX-1 in patients without chronic urticaria. These reactions may be either drug specific or cross-reactive to other NSAIDs.<sup>148</sup> Rarely, some reactions to aspirin or NSAIDs do not fit precisely into these categories and may have blended respiratory and cutaneous reactions.

Allergic rashes are common adverse effects of clopidogrel, a thiopyridine inhibitor of platelet activation that is often recommended in aspirin-intolerant patients. Although the mechanisms of such reactions are unknown, successful oral induction of drug tolerance protocols have been reported.

### Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have 2 major adverse effects—cough and angioedema. Cough occurs in up to 20% of patients, is typically dry and nonproductive, and occurs more commonly in women, blacks, and Asians. The cough generally begins within the first few weeks of treatment, but occasionally the onset may occur much later. Angiotensin receptor blockers (ARBs) are not associated with development of cough.

The incidence of angioedema with ACE inhibitors is approximately 0.1% to 0.7%.<sup>149,150</sup> and appears to be more common in blacks.<sup>151,152</sup> The angioedema frequently involves the face or upper airway and can be life-threatening or fatal.<sup>153,154</sup> Reports of angioedema of the intestinal tract secondary to ACE inhibitors have also been described.<sup>155</sup> Patients with C1 esterase inhibitor deficiency are at increased risk of more frequent and severe episodes of angioedema with the administration of ACE inhibitors and should not receive these drugs. Patients typically take ACE inhibitors for months or even years before angioedema occurs. It is also puzzling that recurrent episodes of angioedema occur sporadically despite continued daily use of ACE inhibitors. Most patients with angioedema related to ACE inhibitor usually tolerate ARBs.<sup>156</sup>

### Biologic Modifiers

In the past decade, a number of biologic agents have been developed to neutralize proinflammatory cytokines, their cel-

Table 3. Classification of Adverse Reactions to Biologics

Type of adverse reaction	Example
High dose	Cytokine release syndrome
Hypersensitivity	Delayed infusion reactions
Secondary Immunodeficiency	Tuberculosis with anti-TNF
Autoimmunity	SLE or vasculitis
Atopic disorders	Atopic dermatitis
Cross-reactivity	Acne from anti-epidermal growth factor receptor
Nonimmunologic adverse effects	Depression from interferons

Abbreviations: SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

lular receptors, and IgE antibody.<sup>157,158</sup> Because the clinical experience with these drugs varies (ie, phase 4 experiences), the spectrum of reported allergic reactions may not yet be fully known for all of them. A separate type of classification for adverse reactions to biological agents has been proposed based on the mechanism of reactions (Table 3).<sup>159</sup> High-dose reactions are related to high cytokine levels administered directly or from cytokines released (cytokine release syndrome). Hypersensitivity reactions may be either antibody or cell-mediated. Immune or cytokine dysregulation may result in secondary immunodeficiency, autoimmunity, or allergic or atopic disorders. Cross-reactive reactions may occur when the biologic agent is intended for a pathologic cell type but cross-reacts with normal cells. Finally, biologics may also result in nonimmunologic adverse effects.

Cytokines, including interferons and anti-tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) drugs, have been reported to cause a variety of drug allergic reactions. Allergic drug reactions ranging from cutaneous lesions to severe anaphylaxis may occur during treatment with recombinant interferons. A variety of immune-mediated reactions have occurred during infliximab (Remicade) treatment for adult and juvenile rheumatoid arthritis, Crohn's disease and psoriasis. These reactions include urticaria, flare-up of atopic dermatitis, maculopapular rashes, leukocytoclastic vasculitis, serum sickness, and at least 7 instances of life-threatening anaphylactic reactions.<sup>160-173</sup> Fewer adverse effects have been associated with adalimumab (Humira), another recently available, fully humanized anti-TNF- $\alpha$  monoclonal antibody. These effects include injection site pruritic rashes and new-onset asthma.<sup>174,175</sup> New-onset asthma may also appear during treatment with both infliximab and etanercept (Enbrel). Immune-mediated reactions have also been rarely associated with the latter agent, a recombinant TNF- $\alpha$  extracellular protein domain fused to human IgG1 Fc, which neutralizes soluble TNF- $\alpha$ . These reactions include urticaria, rashes, injection site reactions, leukocytoclastic vasculitis, lupus erythematosus, and 1 instance of lung granulomatosis injury.<sup>176-182</sup>

Both cutaneous and systemic allergic reactions have been reported after treatment with both murine and humanized monoclonal antibodies. Hypersensitivity reactions to cetux-

imab (chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor), including IgE-mediated anaphylaxis, has been reported to occur at a national rate of 3% or less but much higher (22%) in the Middle South region of the United States.<sup>183</sup> IgE antibodies in this condition are specific for an oligosaccharide galactose- $\alpha$ -1, 3-galactose, which is present on the Fab portion of the cetuximab heavy chain. In most of these patients, specific IgE cetuximab antibodies were present in patients' sera before therapy.<sup>184</sup> Severe symptoms, such as fever, rigors, chills, and acute respiratory distress syndrome, may occur during administration of the first dose of certain monoclonal antibodies due to a cytokine release syndrome.<sup>185,186</sup>

Depending on the monoclonal antibody and type of reaction, readministration strategies may include medication pretreatment, slowing infusion rates, or induction of drug tolerance.<sup>184</sup> In patients with immediate-type reactions, successful induction of tolerance to rituximab, infliximab, and trastuzumab has been reported using a 6-hour protocol in combination with corticosteroid and antihistamine premedication.

Rare anaphylactic reactions to anti-IgE humanized monoclonal antibody (omalizumab) were described during phase 3 clinical trials and during the postmarketing surveillance period. The mechanism of these reactions is unclear. Many cases experienced either delayed-onset (2 hours) or protracted progression of signs and symptoms after dose administration. The Omalizumab Joint Task Force report recommended that patients receiving omalizumab should be directly observed, in a physician's office, after receiving omalizumab for 2 hours after the first 3 doses and 30 minutes after subsequent doses.<sup>187</sup>

### Complementary Medicines

The term *complementary medicine* includes herbal products, vitamins, minerals, amino acids, and essential oils.<sup>188</sup> There is widespread belief that these products are safe because they are "natural."<sup>189</sup> However, well-recognized adverse effects, including anaphylaxis, have been reported in patients using bee pollen products.<sup>190</sup> Allergic reactions, including asthma and anaphylaxis, have been reported after ingestion of echinacea, an herb that is derived from several species of a flowering plant.<sup>191</sup> A variety of cutaneous reactions and 1 instance of TEN have been reported after use of Chinese herbal medications, which sometimes have been adulterated with synthetic medications.<sup>192,193</sup> Because the extent of this problem is unknown, patients should be questioned about the use of herbs and health supplements.

### Other Agents

A number of other agents have been reported to cause drug allergic reactions, including *N*-acetylcysteine, blue dyes, volume expanders, iron-containing dextran, and preservatives. These reactions are discussed further in the text of the parameter.

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## ANNOTATIONS (FIGURE 1):

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

Adverse drug reactions 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 vs viral hepatitis), or a disorder that would not have occurred if the drug had not been used (eg, aseptic necrosis after 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, human immunodeficiency virus–positive patients, or patients with 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).

In making a determination about whether the patient is experiencing an adverse drug reaction, the physician must appreciate the wide scope of such reactions with special emphasis on early recognition, pathophysiologic mechanisms, and severity. Predictable adverse drug reactions (type A) are usually dose dependent and related to the known pharmacologic effects of the drug; examples include pharmacologic adverse effects and drug-drug interactions. Unpredictable reactions (type B) are elicited by relatively small doses and are usually unrelated to the pharmacologic actions of the drug.

In assessing the possibility of an adverse drug reaction, knowledge about the dose, duration of use, temporal relationship of drug administration, and predilection of individual drugs to cause tissue or organ-specific adverse effects is important. In addition, the pharmacologic properties of drugs may provide useful clues about the type of adverse effects 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, from specific drug allergic reactions.

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

A careful history, including a review of all available medical records, is essential. The history should include the following: (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 nonprescription, that the patient is or was 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, sex, race, genetic associations (eg, atopy [usually for reactions to high-molecular-weight biologicals], genetic polymorphisms of HLA-DR, and various drug metabolizing enzymes), and presence of underlying disease (such as human immunodeficiency virus or systemic lupus erythematosus) may support the possibility of a drug allergic reaction.

Because 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. On the basis of the history and physical examination findings, laboratory tests, including differential, blood tests, such as liver or renal function tests, a chest x-ray examination, and/or an electrocardiogram may be advisable. Specific tests that may help to define immunopathogenesis are described in Annotations 5-11.

### **ANNOTATION 3: Consider other possibilities.**

If review of medical history, examination findings, and laboratory test results do not indicate an adverse drug reaction, other causes should be considered. For example, chronic urticaria, non-drug-related contact dermatitis, gastroenteritis, and viral exanthems are often mistaken for adverse drug reactions.

### **ANNOTATION 4: Is drug-induced allergic reaction suspected?**

Once a suspected drug-induced reaction is confirmed, determining whether this reaction is allergic in nature is an important next step. Drug allergy 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/or structure of the drug have been associated with immune reactions; (4) the patient had previously received the drug (or a cross-reacting drug) on 1 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 allergy. The spectrum of drug-induced skin lesions includes urticaria, morbilliform rashes, papulovesicular and bullous eruptions, and exfoliative dermatitis. In addition to cutaneous manifestations, acute life-threatening anaphylactic reactions also may involve the cardiorespiratory and gastrointestinal systems. 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 or tissues.

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Typical examples of drug allergy corresponding to the different types of Gell-Coombs reactions (using penicillin as an example) include (1) urticaria, laryngeal edema, and hypotension immediately after penicillin administration; (2) anemia in a patient receiving large doses of penicillin; (3) fever, arthralgias, lymphadenopathy, and an urticarial rash 7 to 21 days after an injection of penicillin; and (4) maculopapular eruption several days after initiation of penicillin therapy. Patients' presentations may not always be as typical as these examples.

**ANNOTATION 5: The adverse reaction is predictable (eg, toxicity, side effect, drug interaction) or due to idiosyncrasy, intolerance, or pseudoallergic effects of the drug.**

Most adverse drug reactions are predictable type A reactions. Examples of this type of reaction include acetaminophen-induced hepatic toxicity, sedation from antihistamines, and interference of theophylline metabolism by erythromycin. Clinical presentations of idiosyncratic and intolerance reactions are often characteristic for certain drugs. Aspirin-induced tinnitus at therapeutic or subtherapeutic doses is an example of drug intolerance. Hemolytic anemia induced by dapsone in patients with glucose-6-phosphate dehydrogenase deficiency is an example of drug idiosyncrasy. By contrast, pseudoallergic reactions are often symptomatically identical to IgE-mediated drug allergy, may occur without a prior history of exposure, and do not require prior sensitization. Pruritus after administration of opiates is an example of a pseudoallergic reaction. Some but not all nonimmunologic reactions can be confirmed by a graded challenge, including aspirin challenge in patients with possible aspirin-exacerbated respiratory disease.

**ANNOTATION 6: Future management and prevention of nonimmune adverse drug reactions.**

Dose modification may be possible in specific instances of toxicity, adverse effects, or drug interactions. In many cases, use of the drug should be discontinued, and if available, a suitable alternative drug should be used. If the suspect drug is essential, gradually increasing doses of the drug may be administered by various graded challenge regimens in an attempt to minimize adverse effects and to demonstrate tolerance.

Cautious use of some agents inducing severe pseudoallergic reactions (eg, radiocontrast media) may be possible if patients are treated with premedication regimens consisting of corticosteroids and 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 are recommended.

**ANNOTATION 7: Are appropriate confirmatory tests available?**

Diagnosis of many cases of drug allergy is presumptive because specific confirmatory tests are usually not available. Useful clinical testing is predicated on the immunopathogenesis of the drug allergic 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. For low-molecular-weight biologicals, adequate data are not available to determine the predictive value of skin testing except for penicillin. Penicillin and a limited number of other agents (eg, insulin) are the only agents for which optimal negative predictive values for IgE-mediated reactions have been established. Despite this lack of information about predictive values, testing for other agents may provide useful information.

In situations where skin test results 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 optimal negative predictive value. A diagnosis of anaphylaxis may be confirmed by an increase in plasma histamine, serum mature tryptase ( $\beta$ -tryptase), or 24-hour urine *N*-methylhistamine (see Anaphylaxis Practice Parameter).

Immunopathogenesis of delayed drug reactions consistent with type II (cytotoxic) or type III (serum sickness–like) according to the Gell-Coombs classification may be confirmed by nonspecific and specific laboratory tests. Nonspecific tests, such as a complete blood cell 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. The results of specific tests, such as 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 (type IV Gell-Coombs reaction) may be verified by drug-specific (eg, neomycin) epicutaneous patch tests. Because sensitized T cells have been demonstrated in some delayed cutaneous reactions to oral drugs, patch tests to those drugs may also be a helpful diagnostic adjunct. In oral antibiotic-induced delayed cutaneous reactions, drug-specific lymphocyte proliferation and isolation of specific T-cell clones can be demonstrated in some patients. However, the predictive value of such patch testing 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 performing the challenge is thought to be less than the risk of not using the drug. However, such drug challenges are generally contraindicated in cases of severe, life-threat-

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ening immunocytotoxic reactions, such as vasculitic syndromes, exfoliative dermatitis, erythema multiforme major or Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis, hemolytic anemia, and nephritis.

**ANNOTATION 8: Are test results positive?**

A positive immediate hypersensitivity skin test result using a nonirritating concentration of a drug suggests that the patient has specific IgE antibodies to the drug being tested and may be at significant risk for anaphylaxis or less severe immediate hypersensitivity reactions, such as urticaria or angioedema. The positive and negative predictive values of immediate hypersensitivity skin tests are unknown except for few agents. A positive skin test result 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 result is positive, there may be at least a 50% chance of an immediate reaction to penicillin. Positive skin test results to protein agents (eg, insulin, heterologous antisera, streptokinase) generally have good positive predictive value, although few large-scale, prospective studies to determine this index are available. Positive immediate hypersensitivity skin test results to nonirritating concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents. Unfortunately, substantive data are limited on what constitutes a nonirritating concentration for many drugs. A positive in vitro specific IgE reaction to a drug or biological (eg, the major determinant of penicillin, insulin, protamine) and basophil activation tests also indicates significant risk for an immediate reaction, but a negative test result lacks adequate sensitivity to exclude drug allergy. As discussed in Annotation 7, various nonspecific and drug specific tests may help to confirm which immunopathogenic pathway is involved.

**ANNOTATION 9: Diagnosis of drug hypersensitivity and 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 I and IV reactions and occasionally type II reactions. Various nonspecific immunologic tests discussed in Annotation 5 may aid in the diagnosis of type III responses and atypical drug reactions, with clinical manifestations suggesting mixed immunopathogenetic mechanisms. It should be emphasized that skin and 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 10: Management.**

Acute anaphylactic reactions require immediate discontinuation of the drug therapy and prompt emergency measures, as discussed in detail in the Anaphylaxis Practice Parameter.<sup>194</sup>

Documented non-IgE-mediated reactions usually require prompt discontinuation of the drug therapy. If symptoms do not resolve spontaneously, additional symptomatic therapy may be indicated. In the case of immune complex reactions, corticosteroids and antihistamines may be beneficial. In severe cytotoxic or T-cell-mediated reactions, corticosteroids may also be indicated. The use of glucocorticosteroids in advanced stages of the erythema multiforme major or Stevens-Johnson syndrome and TEN is controversial and may increase the risk of infectious complications.

If the drug is determined to be the cause of the reaction, it should be avoided in the future and alternative drugs should be considered. If this is not possible, induction of drug tolerance (eg, desensitization) or graded challenge should be considered. The prophylactic regimens before graded challenge or induction of drug tolerance may be necessary in some cases and are similar to those described in Annotation 4. Readministration of a drug(s) that caused certain severe non-IgE-mediated reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, Churg-Strauss syndrome, and exfoliative dermatitis) is generally contraindicated with rare exceptions, such as when the benefit of treatment of a life-threatening illness outweighs the risk of a potentially life-threatening reaction.

Every effort should be made to prevent allergic reactions to medications. Cross-reactivity between chemically related drugs should be considered. Medications should be prescribed only for medically sound indications, and simultaneous use of multiple drugs should be avoided whenever possible. Orally administered drugs are less likely to produce systemic reactions than drugs given topically or parenterally. For patients with a history of reactions to multiple antibiotics, antibiotics for presumptive diagnosis of respiratory tract infections should be avoided without further testing to confirm the necessity of antimicrobial therapy.

Patients should be carefully instructed about avoiding the drug that caused the reaction or 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, should be fully explained. In such situations, patients should not hesitate to call 911 or other emergency help telephone numbers. MedicAlert jewelry is a useful way of alerting providers about previous drug reactions, thereby preventing inadvertent readministration of the drug.

**ANNOTATION 11: Does test have high negative predictive value?**

If an in vivo or an in vitro test result is negative for specific IgE antibodies directed against the drug, the likelihood that the patient will tolerate the drug depends on the negative predictive value of the test. The negative predictive value for insulin skin testing is good. The only antibiotic for which reliable negative predictive value has been determined is

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penicillin. The negative predictive value of commercial in vitro tests for IgE-mediated penicillin allergy is inferior to skin testing, and they 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 that induce cytotoxic or immune complex reactions.

**ANNOTATION 12: Patient not allergic to this drug.**

Within the limitations discussed in Annotations 7 and 8, a negative test result for IgE-mediated, cytotoxic, immune complex, or contactant hypersensitivity suggests that the patient is not allergic to the suspected drug and the drug may be administered cautiously under observation.

**ANNOTATION 13: Patient may be allergic (despite negative drug-specific or nonspecific confirmatory test results).**

Drug hypersensitivity cannot be confirmed by drug-specific tests in most cases because the positive and negative predictive values have not been determined for most agents. Moreover, comparable data about the allergenicity of the parent compound and its reactive end products or metabolites have only been determined for a few drugs, including penicillin. Because the general availability of tests for cytotoxic drug reactions is limited, a determination of the causal relationship of the drug can usually be made from the history, physical examination, and nonspecific tests. Similarly, only nonspecific laboratory tests can be used for the evaluation of drug-mediated immune complex disease. There are a number of drug reactions for which immunologic mechanisms are strongly suspected but not yet been demonstrated. Thus, the diagnosis of most 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 test results.

**Classification of Recommendations and Evidence**

**Category of evidence:**

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least 1 randomized controlled trial
- IIa Evidence from at least 1 controlled study without randomization
- IIb Evidence from at least 1 other type of quasiexperimental study
- III Evidence from nonexperimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

**Strength of recommendation:**

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated from category I evidence
- C Directly based on category III evidence or extrapolated from category I or II evidence
- D Directly based on category IV evidence or extrapolated from category I, II, or III evidence
- E Based on consensus of the Joint Task Force on Practice Parameters

**SUMMARY STATEMENTS OF THE EVIDENCE-BASED COMMENTARY**

**I. INTRODUCTION**

*Summary Statement 1:* Adverse drug reactions (ADRs) are commonly encountered in both inpatient and outpatient settings and result in major health problems in the United States. (C)

**II. DEFINITIONS**

*Summary Statement 2:* ADRs are broadly categorized into predictable and unpredictable reactions. (D)

*Summary Statement 3:* Unpredictable reactions are subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions. (D)

*Summary Statement 4:* Drug intolerance is an undesirable pharmacologic effect that occurs at low and sometimes subtherapeutic doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. (D)

*Summary Statement 5:* Drug idiosyncrasy is an abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug. (D)

*Summary Statement 6:* Drug allergy reactions are immunologically mediated responses that result in the production of drug-specific antibodies, T cells, or both. (B)

*Summary Statement 7:* Manifestations of pseudoallergic reactions mimic IgE-mediated allergic reactions, but they are due to direct release of mediators from mast cells and basophils and do not require a preceding period of sensitization. (B)

**III. CLASSIFICATION OF IMMUNOLOGICALLY MEDIATED DRUG HYPERSENSITIVITY REACTIONS**

*Summary Statement 8:* Some drug allergic reactions may be classified by the Gell-Coombs classification paradigm of hypersensitivity (type I: IgE mediated; type II: cytotoxic; type III: immune complex; type IV: cell mediated), whereas others cannot be classified because of lack of knowledge of their immunopathogenesis or a mixed mechanism. (C)

*Summary Statement 9:* Allergic drug reactions may also be classified according to the predominant organ system involved (eg, cutaneous, hepatic, renal) or according to the temporal relationship to onset of symptoms (immediate, accelerated, delayed). (D)

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*Summary Statement 10:* To some extent, the structural characteristics of drugs may permit predictions about the type of hypersensitivity reactions they are likely to cause. (C)

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

*Summary Statement 11:* IgE-mediated reactions may occur after administration of a wide variety of drugs, biologicals, and drug formulation agents, with the most common agents being antibiotics. (C)

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

*Summary Statement 12:* Cytotoxic reactions are very serious and potentially life-threatening. (C)

*Summary Statement 13:* Immuno-hemolytic anemias have occurred after treatment with quinidine,  $\alpha$ -methyl dopa, and penicillin. (C)

*Summary Statement 14:* Positive direct and indirect Coombs test results in immuno-hemolytic anemia may reflect the presence of drug-specific IgG, complement, or an Rh determinant autoantibody. (C)

*Summary Statement 15:* Immune-induced thrombocytopenia may result from treatment with heparin, quinidine, propylthiouracil, gold salts, sulfonamides, vancomycin, and other drugs. (C) Platelet membrane damage is mediated mainly by drug-immune serum complexes, which are adsorbed onto platelet membranes. (C)

*Summary Statement 16:* Immune-mediated granulocytopenia is uncommon but may be induced by cytotoxic antibodies synthesized in response to a variety of drugs. (C)

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

*Summary Statement 17:* Immune complex (serum sickness) reactions were originally described with use of heterologous antisera, but they may also be caused by some small-molecular-weight drugs and monoclonal antibodies. (C)

*Summary Statement 18:* The chief manifestations of fever, rash, urticaria, lymphadenopathy, and arthralgias typically appear 1 to 3 weeks after starting use of an offending agent. (C)

*Summary Statement 19:* The prognosis for complete recovery from serum sickness is excellent; however, symptoms may last as long as several weeks. Treatment with systemic corticosteroids and histamine<sub>1</sub> receptor antihistamines may be required. (C)

*Summary Statement 20:* Drug-induced immune complex disease may occur after exposure to heterologous proteins (eg, thymoglobulin) or simple drugs (eg, penicillin, procainamide, phenylpropanolamine). (C)

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

*Summary Statement 21:* Contact dermatitis produced by topical drugs (such as bacitracin, neomycin, glucocorticosteroids, local anesthetics, and antihistamines) and/or excipients contained in topical formulations are due to cell-mediated reactions. (C)

*Summary Statement 22:* It is postulated that Gell-Coombs type IV reactions are also responsible for some delayed

cutaneous maculopapular eruptions due to oral antibiotics, such as amoxicillin and sulfonamides. (C)

*Summary Statement 23:* Patch testing at proper concentrations may be successful in detection of suspected contact allergens. (B)

*Summary Statement 24:* After avoidance is instituted, topical and/or systemic corticosteroids may be required for total clearing of the dermatitis (provided that these drugs were not the primary causes). (C)

#### **E. Miscellaneous Syndromes**

*Summary Statement 25:* Some drugs or classes of drugs are associated with characteristic syndromes that often do not conform to specific Gell-Coombs categories and sometimes are referred to as mixed drug reactions (ie, a mixture of immunologic mechanism). (C)

*Summary Statement 26:* Many drugs, hematopoietic growth factors, cytokines, and interferons are associated with vasculitis of skin and visceral organs. (C)

*Summary Statement 27:* The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced, multiorgan inflammatory response that may be life-threatening. First described in conjunction with anticonvulsant drug use, it has since been ascribed to a variety of drugs. (C)

*Summary Statement 28:* Anticonvulsant hypersensitivity syndrome is mainly associated with aromatic anticonvulsant drugs and is related to an inherited deficiency of epoxide hydrolase, an enzyme required for the metabolism of arene oxide intermediates produced during hepatic metabolism. (B) Phenytoin, carbamazepine, and phenobarbital are considered cross-reactive, but valproic acid, gabapentin, and lamotrigine are therapeutic alternatives. (C) It is slower in onset than DRESS and presents with skin nodules, plaques, and lymphadenopathy at times confused with lymphoreticular malignant tumors (ie, pseudolymphoma). (B)

*Summary Statement 29:* Pulmonary manifestations of allergic drug reactions include anaphylaxis, lupuslike reactions, alveolar or interstitial pneumonitis, noncardiogenic pulmonary edema, and granulomatous vasculitis (ie, Churg-Strauss syndrome). Specific drugs are associated with different types of pulmonary reactions, such as bleomycin-induced fibrosis. (C)

*Summary Statement 30:* Drug-induced lupus erythematosus (DILE) can have systemic forms and predominantly cutaneous forms. Procainamide and hydralazine are the most frequently implicated drugs for systemic DILE, and antihistone antibodies are present in more than 90% of patients but occur less commonly with minocycline, propylthiouracil, and statins. (C)

*Summary Statement 31:* Drugs most commonly associated with cutaneous DILE include hydrochlorothiazide, calcium channel blockers, angiotensin-converting enzyme inhibitors, and systemic antifungal agents. Anti-Ro and anti-SSA antibodies are usually present, whereas antihistone antibodies are much less frequent. (C)

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*Summary Statement 32:* The recognition of immunologically mediated, drug-induced granulomatous disease with or without vasculitis has increased in recent years. (C)

*Summary Statement 33:* Immunologic hepatitis may occur after sensitization to para-aminosalicylic acid, sulfonamides, and phenothiazines. (C)

*Summary Statement 34:* Erythema multiforme minor is a cell-mediated hypersensitivity reaction associated with viruses, other infectious agents, and drugs. It manifests as pleomorphic cutaneous eruptions, with target lesions being most characteristic. (C)

*Summary Statement 35:* There is no consensus on the distinction between erythema multiforme major and Stevens-Johnson syndrome. These disorders involve mucosal surfaces as well as the skin. (D)

*Summary Statement 36:* Use of systemic corticosteroids for treatment of erythema multiforme major or Stevens-Johnson syndrome is controversial. (D)

*Summary Statement 37:* Toxic epidermal necrolysis (ie, Lyell syndrome) is distinguished from Stevens-Johnson syndrome by the extent of epidermal detachment. (D)

*Summary Statement 38:* Systemic corticosteroids are associated with increased mortality when used for the management of advanced toxic epidermal necrolysis (C). Treatment with high-dose intravenous immunoglobulin is controversial. (D)

*Summary Statement 39:* Toxic epidermal necrolysis should be managed in a burn unit. (D)

*Summary Statement 40:* Serum sickness-like reactions caused by cephalosporins (especially cefaclor) usually are due to altered metabolism of the drug, resulting in reactive intermediates. (B)

*Summary Statement 41:* Immunologically mediated nephropathies may present as interstitial nephritis (such as with methicillin) or as membranous glomerulonephritis (eg, gold, penicillamine, and allopurinol). (C)

#### **F. Other Classification Systems for Drug Allergy**

*Summary Statement 42:* In addition to Gell-Coombs hypersensitivity reactions, there are a number of other mechanistic and clinical classifications for drug allergy. (C)

*Summary Statement 43:* The p-i concept (pharmacologic interaction with immune receptors) is a recently proposed addition to drug hypersensitivity classification in which a drug binds noncovalently to a T-cell receptor, which may lead to an immune response via interaction with a major histocompatibility complex receptor. (C)

*Summary Statement 44:* From a clinical standpoint, the most practical method of classifying drug reactions is by predilection for various tissue and organ systems. (D)

*Summary Statement 45:* The structural characteristics of drugs and biological products may permit predictions about what type of hypersensitivity reactions to expect from certain classes of therapeutic substances. (C)

#### **IV. RISK FACTORS**

*Summary Statement 46:* The most important risk factors for drug hypersensitivity may be related to the chemical property and molecular weight of drugs. (C)

*Summary Statement 47:* Other drug-specific risk factors for drug hypersensitivity include the dose, route of administration, duration of treatment, repetitive exposure to the drug, and concurrent illnesses (eg, Epstein-Barr virus infection and amoxicillin rash). (C)

*Summary Statement 48:* Host risk factors for drug hypersensitivity include age, sex, atopy, underlying diseases (such as lupus erythematosus and human immunodeficiency virus), and specific genetic polymorphisms. (C)

#### **V. CLINICAL EVALUATION AND DIAGNOSIS OF DRUG ALLERGY**

*Summary Statement 49:* The history should focus on previous and current drug use and the temporal sequence of events between initiation of therapy and onset of symptoms. (C)

*Summary Statement 50:* Physical examination should include all systems that could possibly account for the clinical presentation. (C)

*Summary Statement 51:* Cutaneous manifestations are the most common presentation for drug allergic reactions. Characterization of cutaneous lesions is important in regard to determining the cause, further diagnostic tests, and management decisions. (C)

*Summary Statement 52:* Numerous cutaneous reaction patterns have been reported in drug allergy, including exanthems, urticaria, angioedema, acne, bullous eruptions, fixed drug eruptions, erythema multiforme, lupus erythematosus, photosensitivity, psoriasis, purpura, vasculitis, pruritus, and life-threatening cutaneous reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and drug rash with eosinophilia and systemic symptoms (DRESS). (C)

*Summary Statement 53:* Possible laboratory tests might include but are not limited to a chest x-ray examination, electrocardiography, a complete blood cell count with differential, sedimentation rate or C-reactive protein, autoantibody tests, and specific immunologic tests. (C)

*Summary Statement 54:* The most useful test for detecting IgE-mediated drug reactions caused by penicillin and many large-molecular-weight biologicals is immediate hypersensitivity skin testing. (B)

*Summary Statement 55:* Specialized immunologic tests are sometimes able to confirm the immunologic basis of drug-induced cytotoxic reactions. (B)

*Summary Statement 56:* Drug patch testing may be useful for certain types of cutaneous drug reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions, but generally is not helpful for Stevens-Johnson syndrome or urticarial eruptions. The lack of standardization of reagent concentrations may limit the clinical usefulness of drug patch testing. (B)

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*Summary Statement 57:* Lymphocyte proliferation assays may have utility as retrospective indicators of cell-mediated drug reactions, but their positive and negative predictive values have not been determined and they are not available in most medical centers. (C)

*Summary Statement 58:* In complex cases where multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy may be useful in suggesting a drug-induced eruption. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy may not definitively exclude alternative causes. (C)

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

*Summary Statement 59:* Ideally ADRs should be prevented. Steps to prevent allergic drug reactions include (1) a careful history to determine host risk factors, (2) avoidance of cross-reactive drugs, (3) use of predictive tests when available, (4) proper and prudent prescribing of drugs (especially antibiotics) that are frequently associated with adverse reactions, (5) use of oral drugs when possible, and (6) documentation of ADR in the patient's medical record. (D)

*Summary Statement 60:* For some allergic drug reactions, withdrawal of the drug may be all that is required for treatment. (C)

*Summary Statement 61:* Anaphylactic drug reactions require prompt emergency treatment as discussed extensively in "The Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter." (B)

*Summary Statement 62:* Glucocorticosteroids may be required for immune complex reactions, drug-induced hematologic diseases, early stages of erythema multiforme major/Stevens-Johnson syndrome, and contact sensitivities. (C)

*Summary Statement 63:* What has often been referred to as drug desensitization is more appropriately described in this parameter as a temporary induction of drug tolerance. (D)

*Summary Statement 64:* Induction of drug tolerance modifies a patient's response to a drug to temporarily allow treatment with it safely. It is only indicated in situations where an alternate non-cross-reacting medication cannot be used. (B)

*Summary Statement 65:* Through various mechanisms, induction of drug tolerance procedures induces a temporary state of tolerance to the drug that is maintained only as long as the patient continues to take the specific drug. (B)

*Summary Statement 66:* Immunologic IgE induction of drug tolerance (drug desensitization) is the progressive administration of an allergenic substance to render effector cells less reactive. These procedures typically are performed within hours, and the typical starting dose is in the microgram range. (B)

*Summary Statement 67:* For some delayed non-IgE-mediated cutaneous reactions, immunologic non-IgE induction of drug tolerance may be performed to allow treatment with the drug. However, it is generally contraindicated, with rare exceptions, for serious non-IgE-mediated reactions, such as

Stevens-Johnson syndrome or toxic epidermal necrolysis. One example of when the benefit of treatment may outweigh the risk of reaction is imatinib for treatment of malignant tumors. (C)

*Summary Statement 68:* Pharmacologic induction of drug tolerance to aspirin (eg, aspirin desensitization) is primarily intended for patients with AERD, and unlike other types of desensitization, its purpose is to cautiously induce (rather than prevent) a reaction, after which patients become tolerant of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). (B)

*Summary Statement 69:* Some induction of drug tolerance procedures have been described that appear to be successful through currently undefined mechanisms. (C)

*Summary Statement 70:* The objective of a graded challenge is to cautiously introduce a drug in patients who are unlikely to be allergic to it. Unlike induction of drug tolerance, it does not modify patients' response to a drug. (D)

## **VII. SPECIFIC DRUGS**

### **A. $\beta$ -Lactam Antibiotics**

#### **1. Penicillin**

*Summary Statement 71:* Approximately 10% of patients report a history of penicillin allergy, but after complete evaluation, up to 90% of these individuals are able to tolerate penicillins. (B)

*Summary Statement 72:* Treatment of patients assumed to be penicillin allergic with alternate broad-spectrum antibiotics may compromise optimal medical care by leading to multiple drug-resistant organisms, higher costs, and increased toxic effects. (C)

*Summary Statement 73:* Evaluation of patients with penicillin allergy by skin testing leads to reduction in the use of broad-spectrum antibiotics and may decrease costs. (B)

*Summary Statement 74:* The rate of penicillin-induced anaphylaxis after parenteral administration is approximately 1 to 2 per 10,000 treated patients. (C)

*Summary Statement 75:* Penicillin is immunologically inert and haptens proteins after undergoing spontaneous conversion under physiologic conditions to reactive intermediates. These transformation products are known as penicillin major and minor antigenic determinants. (C)

*Summary Statement 76:* Penicillin skin testing is the most reliable method for evaluating IgE-mediated penicillin allergy. (B) Ideally, penicillin skin testing should be performed with both major and minor determinants. The negative predictive value of penicillin skin testing for immediate reactions approaches 100%, whereas the positive predictive value is between 40% and 100%. (B)

*Summary Statement 77:* Skin testing with the major determinant and penicillin G only (without penicilloate or penicilloate) may miss up to 20% of allergic patients, but data on this are conflicting. (C)

*Summary Statement 78:* Penicillin G left in solution ("aged" penicillin) does not spontaneously degrade to form

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antigenic determinants and has no role in penicillin skin testing. (B)

*Summary Statement 79:* Penicillin skin testing without the major determinant is not recommended because this would fail to identify many patients with penicillin specific IgE antibodies. (B)

*Summary Statement 80:* When performed by skilled personnel using proper technique, serious reactions due to penicillin skin testing are extremely rare. (C)

*Summary Statement 81:* Penicillin skin testing may be performed electively—when patients are well and not in immediate need of antibiotic therapy. Alternatively, penicillin skin testing may be performed when treatment with a penicillin compound is contemplated. (D)

*Summary Statement 82:* Patients who have had negative skin test results to penicillin major and minor determinants may receive penicillin with minimal risk of an IgE-mediated reaction. Depending on the reaction history, the first dose may need to be given via graded challenge. (D)

*Summary Statement 83:* Penicillin skin test–positive patients should avoid penicillin, but if they develop an absolute need for penicillin, rapid induction of drug tolerance may be performed. (B)

*Summary Statement 84:* Resensitization after treatment with oral penicillin is rare, and therefore penicillin skin testing does not routinely need to be repeated in patients with a history of penicillin allergy who have tolerated 1 or more courses of oral penicillin. (B)

*Summary Statement 85:* Resensitization after treatment with parenteral penicillin appears to be higher than for oral treatment, and therefore repeat penicillin skin testing may be considered in patients with a history of penicillin allergy who have tolerated a course of parenteral penicillin. (C)

*Summary Statement 86:* The negative predictive value of penicillin skin testing without penicilloylpolylysine is poor because many allergic patients show skin test reactivity only to the major determinant. (B)

*Summary Statement 87:* When penicillin skin testing is unavailable, evaluation of penicillin allergy is based on the reaction history and likelihood of needing treatment with penicillins. (C)

*Summary Statement 88:* Patients with a vague and/or distant history of penicillin allergy may be candidates to receive penicillins via graded challenge. Patients with recent or convincing reaction histories should only receive penicillins via rapid induction of drug tolerance. (C)

*Summary Statement 89:* The usefulness of in vitro tests for penicillin specific IgE is limited by their uncertain predictive value. They are not suitable substitutes for penicillin skin testing. (C)

## **2. Ampicillin and amoxicillin**

*Summary Statement 90:* Some patients with immediate-type reactions to amoxicillin and ampicillin have IgE antibodies directed at the R-group side chain (rather than the core

penicillin determinants) and are able to tolerate other penicillin class compounds. (C)

*Summary Statement 91:* Amoxicillin and ampicillin are associated with the development of a delayed maculopapular rash in approximately 5% to 10% of patients. (C) These reactions are not related to IgE-mediated allergy, and they are postulated in many cases to require the presence of a concurrent viral infection or another underlying illness. (D)

## **3. Cephalosporins**

*Summary Statement 92:* The overall reaction rate to cephalosporins is approximately 10-fold lower than it is for penicillin. (C)

*Summary Statement 93:* Most hypersensitivity reactions to cephalosporins are probably directed at the R-group side chains rather than the core  $\beta$ -lactam portion of the molecule. (D)

*Summary Statement 94:* Skin testing with native cephalosporins is not standardized, but a positive skin test result using a nonirritating concentration suggests the presence of drug specific IgE antibodies. (D) A negative skin test result does not rule out an allergy because the negative predictive value is unknown. (D)

*Summary Statement 95:* Patients with a history of an immediate-type reaction to 1 cephalosporin should avoid cephalosporins with similar R-group side chains. (D) Treatment with cephalosporins with dissimilar side chains may be considered, but the first dose should be given via graded challenge or induction of drug tolerance, depending on the severity of the previous reaction. (D)

*Summary Statement 96:* Cephalosporins and penicillins share a common  $\beta$ -lactam ring structure and moderate cross-reactivity has been documented in vitro. (B)

## **4. Cephalosporin administration to patients with a history of penicillin allergy**

*Summary Statement 97:* Since 1980, studies show that approximately 2% of penicillin skin test–positive patients react to treatment with cephalosporins, but some of these reactions may be anaphylactic reactions. (C)

*Summary Statement 98:* Without preceding penicillin skin testing, cephalosporin treatment of patients with a history of penicillin allergy, selecting out those with severe reaction histories, show a reaction rate of 0.1% based on recent studies. (C)

*Summary Statement 99:* Penicillin skin testing, when available, should be considered before administration of cephalosporins in patients with a history of penicillin allergy. (E)

*Summary Statement 100:* Patients who have a history of a possible IgE-mediated reaction to penicillin, regardless of the severity of the reaction, may receive cephalosporins with minimal concern about an immediate reaction if skin test results for penicillin major and minor determinants are negative. (B)

*Summary Statement 101:* Treatment options for penicillin skin test–positive patients include (1) administration of an

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alternate (non- $\beta$ -lactam) antibiotic, (2) administration of cephalosporin via graded challenge, or (3) administration of cephalosporin via rapid induction of drug tolerance. (E)

*Summary Statement 102:* Skin testing to the cephalosporin followed by graded challenge appears to be a safe method for administration of some cephalosporins in penicillin allergic patients. (B)

*Summary Statement 103:* If penicillin and cephalosporin skin testing is unavailable, depending on the reaction history, cephalosporins may need to be given via graded challenge or rapid induction of drug tolerance. (E)

## 5. Penicillin administration to patients with a history of cephalosporin allergy

*Summary Statement 104:* Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine) or receive them via rapid induction of drug tolerance. (C) Similarly, patients allergic to ampicillin should avoid cephalosporins and carbapenems with identical R-group side chains (cephalexin, cefaclor, cephadrine, cephaloglycin, loracarbef) or receive them via rapid induction of drug tolerance. (C)

*Summary Statement 105:* Patients with a history of an immediate-type reaction to a cephalosporin should undergo penicillin skin testing, if available, before treatment with penicillin. (E) If test results are negative, they may safely receive penicillins. (B) If test results are positive, an alternate drug should be used or they should undergo rapid penicillin induction of drug tolerance. (B) If penicillin skin testing is unavailable, penicillin may be administered via cautious graded challenge. (C)

## 6. Monobactams (aztreonam)

*Summary Statement 106:* Aztreonam is less immunogenic than penicillin and cephalosporins, and clinical allergic reactions to aztreonam are less common than other  $\beta$ -lactam antibiotics. (C)

*Summary Statement 107:* Aztreonam does not cross-react with other  $\beta$ -lactams except for ceftazidime, with which it shares an identical R-group side chain. (B)

## 7. Carbapenems

*Summary Statement 108:* Limited data indicate lack of significant allergic cross-reactivity between penicillin and carbapenems. (B) Penicillin skin test–negative patients may safely receive carbapenems. (C) Penicillin skin test–positive patients and patients with a history of penicillin allergy who do not undergo skin testing should receive carbapenems via graded challenge. (C)

## B. Non- $\beta$ -Lactam Antibiotics

*Summary Statement 109:* Any non- $\beta$ -lactam antibiotic has the potential of causing an IgE-mediated reaction, but these appear to occur less commonly than with  $\beta$ -lactam antibiotics. (C)

*Summary Statement 110:* There are no validated diagnostic tests for evaluation of IgE-mediated allergy to non- $\beta$ -lactam

antibiotics. (C) Evaluation of possible allergy to these antibiotics should be limited to situations when treatment with the drug is anticipated (rather than electively as for penicillin). (D)

*Summary Statement 111:* Skin testing with nonirritating concentrations of non- $\beta$ -lactam antibiotics is not standardized. A negative skin test result does not rule out the possibility of an immediate-type allergy. A positive skin test result suggests the presence of drug specific IgE antibodies, but the predictive value is unknown. (D)

*Summary Statement 112:* Patients with a history of reactions to non- $\beta$ -lactam antibiotics consistent with an IgE-mediated mechanism should only receive them if an alternate agent cannot be substituted and only via rapid induction of drug tolerance. (D)

*Summary Statement 113:* Sulfonamide antibiotics rarely cause IgE-mediated reactions and more commonly result in delayed maculopapular rashes, particularly in human immunodeficiency virus–positive patients. (C)

*Summary Statement 114:* There is no evidence to suggest allergic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides. (C)

*Summary Statement 115:* Vancomycin rarely causes IgE-mediated reactions, but more than 50% of patients experience immediate cutaneous erythema, flushing, and pruritus (red man syndrome), which is the result of non-IgE-mediated histamine release. (C)

*Summary Statement 116:* Red man syndrome reactions can be prevented by slowing the rate of infusion and premedicating with histamine<sub>1</sub> receptor antihistamines. (C)

*Summary Statement 117:* Aminoglycosides rarely cause drug allergic reactions, including IgE-mediated systemic reactions. (C)

*Summary Statement 118:* IgE-mediated and non-IgE-mediated anaphylactic reactions have been reported with quinolones. In vitro studies suggest a large extent of allergic cross-reactivity among quinolones, but there are no clinical studies to confirm this. (C)

*Summary Statement 119:* Anaphylactic or anaphylactoid reactions during the operative and perioperative periods may be caused by induction agents, muscle-relaxing agents, opiates, antibiotics, and latex allergy. (C)

## C. Antimycobacterial Drugs

*Summary Statement 120:* Allergic drug reactions to antimycobacterial drugs present significant problems in the implementation of long-term treatment regimens and preventing drug resistance to *Mycobacterium tuberculosis*. (C)

## D. Diabetes Medications

*Summary Statement 121:* The advent of human recombinant insulin has greatly reduced the incidence of life-threatening allergic reactions to approximately 1%. (C)

*Summary Statement 122:* Metformin and sulfonylurea antidiabetic drugs rarely cause immune-mediated reactions, such as leukocytoclastic vasculitis, generalized arteritis, gran-

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ulomatous hepatitis, and autoimmune pemphigus vulgaris. (C)

### **E. Cancer Chemotherapeutics**

*Summary Statement 123:* Cancer chemotherapeutic agents, such as taxanes (paclitaxel, docetaxel), platinum compounds (cisplatin, carboplatin, oxaliplatin), and asparaginase, may cause severe immediate-type reactions, which may be either anaphylactic or anaphylactoid in nature. (C)

*Summary Statement 124:* For some chemotherapeutics (primarily the platinum-based compounds), skin testing may assist in identifying allergic patients who are at increased risk for an allergic reaction and for confirming IgE-mediated sensitivity. (C)

*Summary Statement 125:* Rapid induction of drug tolerance protocols are available for most chemotherapeutic agents that cause immediate-type reactions, but they are not uniformly successful. (C)

*Summary Statement 126:* Methotrexate can cause interstitial reactions in the lungs, which can progress to fibrosis if use of the drug is continued. (C)

### **F. Human Immunodeficiency Virus (HIV) Medications**

*Summary Statement 127:* Patients infected with HIV have an increased frequency of adverse reactions to a variety of drugs, and the pathogenesis of these reactions is likely multifactorial. (C)

*Summary Statement 128:* The most common ADR in HIV-positive patients who take trimethoprim-sulfamethoxazole is a morbilliform and/or maculopapular eruption, often associated with fever that occurs after 7 to 12 days of therapy. (C)

*Summary Statement 129:* HIV-positive patients who have experienced typical delayed exanthematous reactions to trimethoprim-sulfamethoxazole and who require treatment with the drug (such as for *Pneumocystis carinii* pneumonia) may undergo one of several published trimethoprim-sulfamethoxazole induction of drug tolerance protocols. (D) Usually, this should be done after waiting for at least 1 month after the reaction to increase the likelihood of success. (D)

*Summary Statement 130:* Reintroduction of trimethoprim-sulfamethoxazole in HIV-positive patients with a history of more severe reactions to trimethoprim-sulfamethoxazole, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, is generally contraindicated, with rare exceptions, such as treatment of a life-threatening infection, in which case the benefit of treatment outweighs the risk of a potentially life-threatening reaction. (D)

*Summary Statement 131:* Antiretroviral drugs used for highly active antiretroviral therapy (HAART) of HIV-infected patients may cause allergic reactions of various kinds. (C)

*Summary Statement 132:* Abacavir is the most common HAART drug to cause severe allergic reactions, and this risk is associated with the presence of HLA B 5701. (C)

### **G. Disease-Modifying Antirheumatic Drugs (DMARDs)**

*Summary Statement 133:* Apart from adverse reactions to aspirin, other NSAIDs, and certain pyrazolone derivatives (discussed in VII-R), a variety of allergic reactions to other DMARDs may occur. (C)

### **H. Modifying Drugs for Dermatologic Diseases**

*Summary Statement 134:* Although hypersensitivity reactions to several unique therapeutic agents for autoimmune diseases have already occurred, it is too early to assess the global impact of adverse events for diverse immunologic interventions in early development. (C)

### **I. Immunomodulatory Agents for Autoimmune Diseases**

*Summary Statement 135:* Allergic reactions to immunosuppressant and anti-inflammatory drugs are commonly encountered in the treatment of chronic cutaneous diseases. (C)

### **J. Perioperative Agents**

*Summary Statement 136:* Anaphylactic or anaphylactoid reactions during the operative and perioperative periods may be caused by induction agents, muscle-relaxing agents, opiates, antibiotics, and latex allergy. (C)

### **K. Blood and Blood Products**

*Summary Statement 137:* Reactions due to blood and blood products include urticaria, anaphylaxis (particularly in patients with complete IgA deficiency), anaphylactoid reactions, and transfusion-related acute lung injury (TRALI). (C)

### **L. Opiates**

*Summary Statement 138:* Opiates and their analogs are a common cause of pseudoallergic reactions that are generally mild, are not life-threatening, and can be attenuated by preadministration of histamine<sub>1</sub> receptor antihistamines. (C)

### **M. Corticosteroids**

*Summary Statement 139:* Immediate-type reactions to corticosteroids are rare and may be either anaphylactic or anaphylactoid in nature. (C)

*Summary Statement 140:* Most reported reactions to corticosteroids involved intravenous methylprednisolone and hydrocortisone, and preservatives and diluents have also been implicated. (C)

### **N. Protamine**

*Summary Statement 141:* Severe immediate reactions may occur in patients receiving protamine for reversal of heparinization. (C)

*Summary Statement 142:* Diabetic patients receiving protamine-containing insulin are at greatest risk of severe reactions due to intravenous protamine. (C)

### **O. Heparin**

*Summary Statement 143:* Hypersensitivity reactions to unfractionated heparin and low-molecular-weight heparin are uncommon and include thrombocytopenia, various cutaneous eruptions, hypereosinophilia, and anaphylaxis. (C)

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## P. Local Anesthetics

*Summary Statement 144:* Most adverse reactions to local anesthetics are not due to IgE-mediated mechanisms but are due to nonallergic factors that include vasovagal responses, anxiety, toxic reactions including dysrhythmias, and toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine effects. (C)

*Summary Statement 145:* To exclude the rare possibility of an IgE-mediated reaction to local anesthetics, skin testing and graded challenge can be performed in patients who present with a reaction history suggestive of possible IgE-mediated allergy to these drugs. (B)

## Q. Radiocontrast Media (RCM)

*Summary Statement 146:* Anaphylactoid reactions occur in approximately 1% to 3% of patients who receive ionic RCM and less than 0.5% of patients who receive nonionic RCM. (C)

*Summary Statement 147:* Risk factors for anaphylactoid reactions to RCM include female sex, atopy, concomitant use of  $\beta$ -blocking drugs, and a history of previous reactions to RCM. (C)

*Summary Statement 148:* Although asthma is associated with an increased risk of a RCM reaction, specific sensitivity to seafood (which is mediated by IgE directed to proteins) does not further increase this risk. There is no evidence that sensitivity to iodine predisposes patients to RCM reactions. (C)

*Summary Statement 149:* Patients who experienced previous anaphylactoid reactions to RCM should receive nonionic, iso-osmolar agents and be treated with a premedication regimen, including systemic corticosteroids and histamine<sub>1</sub> receptor antihistamines; this will significantly reduce, but not eliminate, the risk of anaphylactoid reaction with re-exposure to contrast material. (D)

*Summary Statement 150:* Delayed reactions to RCM, defined as reactions occurring 1 hour to 1 week after administration, occur in approximately 2% patients. (C) Most are mild, self-limited cutaneous eruptions that appear to be T-cell mediated, although more serious reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS syndrome have been described.

## R. Aspirin and Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

*Summary Statement 151:* One type of adverse reaction to aspirin/NSAIDs is AERD, a clinical entity characterized by aspirin- and NSAID-induced respiratory reactions in patients with underlying asthma and/or rhinitis or sinusitis. (B)

*Summary Statement 152:* The mechanism of AERD appears to be related to aberrant arachidonic acid metabolism. (B)

*Summary Statement 153:* Controlled oral provocation with aspirin is considered to be the most conclusive way to confirm the diagnosis of AERD. (B)

*Summary Statement 154:* Aspirin and NSAIDs that inhibit cyclooxygenase 1 (COX-1) cross-react and cause respiratory reactions in AERD, whereas selective COX-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely. (B)

*Summary Statement 155:* Aspirin desensitization followed by daily aspirin therapy to perpetuate the aspirin tolerant state in patients with AERD is indicated in patients with AERD if aspirin or NSAIDs are therapeutically necessary for treatment of some other condition, such as cardiac or rheumatologic diseases. (D)

*Summary Statement 156:* Aspirin desensitization followed by daily aspirin has been associated with improved outcomes in patients with AERD who are poorly controlled with medical and/or surgical management. (D)

*Summary Statement 157:* A second reaction type to aspirin and NSAIDs is exacerbation of urticaria and angioedema in approximately 20% to 40% of patients with underlying chronic idiopathic urticaria. (C) Drugs that inhibit COX-1 cross-react to cause this reaction, whereas selective COX-2 inhibitors typically are better tolerated by these patients. (C)

*Summary Statement 158:* A third reaction type to aspirin and NSAIDs is suggestive of an IgE-mediated mechanism and manifests as urticaria or angioedema or anaphylaxis, and it occurs in patients with no underlying respiratory or cutaneous disease. (C) These reactions appear to be drug specific, and there is no cross-reactivity with other NSAIDs. (D)

*Summary Statement 159:* A fourth reaction type to aspirin and NSAIDs is urticaria or angioedema caused by all drugs that inhibit COX-1, and it occurs in patients without a prior history of chronic urticaria. (C)

*Summary Statement 160:* Rarely, patients exhibit combined (“blended”) respiratory and cutaneous reaction to aspirin or NSAIDs and hence cannot be classified into 1 of the 4 reaction types described above. (C)

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

*Summary Statement 161:* ACE inhibitors are associated with 2 major adverse effects—cough and angioedema. (C)

*Summary Statement 162:* ACE inhibitor–related cough often begins within the first few weeks of treatment and occurs in up to 20% of patients, particularly women, blacks, and Asians. (C)

*Summary Statement 163:* The mechanism of ACE inhibitor–related cough is unclear. The cough resolves with discontinuation of the drug therapy in days to weeks. (D)

*Summary Statement 164:* Patients with ACE inhibitor–related cough are able to tolerate angiotensin receptor blockers (ARBs). (A)

*Summary Statement 165:* ACE inhibitor–induced angioedema occurs in approximately 0.1% to 0.7% of patients and is most common in blacks. (C)

*Summary Statement 166:* ACE inhibitor–induced angioedema frequently involves the face and oropharynx and can be life-threatening or fatal. (C)

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*Summary Statement 167:* The mechanism of ACE inhibitor-induced angioedema may be related to interference with bradykinin degradation. It may take months or years after initiation of therapy for a reaction to appear and often occurs sporadically despite persistent treatment. (C)

*Summary Statement 168:* ACE inhibitor-induced angioedema is treated with discontinuation of the drug therapy and subsequent avoidance of all ACE inhibitors. (D)

*Summary Statement 169:* Most patients who experience angioedema during ACE inhibitor treatment are able to tolerate ARBs. (C)

*Summary Statement 170:* Patients with a history of angioedema or C1 esterase inhibitor deficiency are at increased risk of more frequent and severe episodes of angioedema with the administration of ACE inhibitors, so they should not receive these drugs. (C)

## T. Biologic Modifiers

*Summary Statement 171:* Allergic drug reactions ranging from cutaneous lesions to severe anaphylaxis may occur during treatment with recombinant interferons. (C)

*Summary Statement 172:* Both cutaneous and systemic allergic reactions have been reported after treatment with infliximab, a human monoclonal antibody against tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). (C)

*Summary Statement 173:* Both cutaneous and systemic allergic reactions have been reported after treatment with both murine and humanized monoclonal antibodies. (C)

*Summary Statement 174:* Rare anaphylactic reactions to anti-IgE humanized monoclonal antibody (omalizumab) were described during phase III clinical trials and during the post-marketing surveillance period. (C)

*Summary Statement 175:* The cytokine release syndrome must be distinguished between anaphylactoid and anaphylactic reactions due to anticancer monoclonal antibodies. (C)

## U. Complementary Medicines

*Summary Statement 176:* Allergic reactions may occur after use of complementary medicines such as bee pollen, echinacea, and vitamins. (C)

## V. Other Agents

*Summary Statement 177:* N-acetylcysteine may cause anaphylactoid reactions. (C)

*Summary Statement 178:* Anaphylactoid reactions and deaths have been associated with intravenous iron preparations, particularly iron-dextran. (C)

*Summary Statement 179:* Life-threatening anaphylactic reactions have occurred after intravenous use of isosulfan blue and Patent Blue V dyes. (C)

*Summary Statement 180:* Anaphylactoid reactions may occur after treatment with colloid volume expanders, mannitol, Cremophor-EL, and preservatives. (C)

*Summary Statement 181:* Preservatives and additives in medications rarely cause immunologic drug reactions. (C)

## EVIDENCE-BASED COMMENTARY

### I. INTRODUCTION

*Summary Statement 1:* Adverse drug reactions (ADRs) are commonly encountered in both inpatient and outpatient settings and result in major health problems in the United States. (C)

ADRs result in major health problems in the United States. In a meta-analysis of inpatient ADR prospective studies, 15.1% of patients sustained ADRs, and 6.7% of patients experienced serious ADRs.<sup>195</sup> Using the same data, the authors estimated that inpatient ADRs are responsible for 106,000 deaths annually in the United States. Depending on whether one uses the lower or upper limit of this confidence interval, inpatient ADRs constitute either the fourth or sixth leading cause of death in the United States.<sup>195</sup>

Although most drugs are prescribed for outpatients, few studies have evaluated the frequency and severity of ADRs in this setting. In a 4-week, prospective cohort study of outpatients followed up in primary care clinics, 25% of patients reported ADRs, 13% of which were serious.<sup>196</sup> In another retrospective study, 17% of outpatients reported ADRs due to a prescribed medication.<sup>197</sup>

### II. DEFINITIONS

*Summary Statement 2:* ADRs are broadly categorized into predictable and unpredictable reactions. (D)

*Summary Statement 3:* Unpredictable reactions are subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions. (D)

*Summary Statement 4:* Drug intolerance is an undesirable pharmacologic effect that occurs at low and sometimes subtherapeutic doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. (D)

*Summary Statement 5:* Drug idiosyncrasy is an abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug. (D)

*Summary Statement 6:* Drug allergy reactions are immunologically mediated responses that result in the production of drug-specific antibodies, T cells, or both. (B)

*Summary Statement 7:* Manifestations of pseudoallergic reactions mimic IgE-mediated allergic reactions, but they are due to direct release of mediators from mast cells and basophils and do not require a preceding period of sensitization. (B)

ADRs are broadly categorized into predictable and unpredictable reactions.<sup>198</sup> Predictable reactions are usually dose dependent, are related to the known pharmacologic actions of the drug, and occur in otherwise healthy individuals. They are estimated to comprise approximately 80% of all ADRs. Unpredictable reactions are generally dose independent, are unrelated to the pharmacologic actions of the drug, and occur only in susceptible individuals. Unpredictable reactions are subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions.

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Drug intolerance is an undesirable pharmacologic effect that occurs at low and sometimes subtherapeutic doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. Humoral or cellular immune mechanisms are not thought to be involved, and a scientific explanation for such exaggerated responses has not been established. A typical example is aspirin-induced tinnitus occurring at usual therapeutic or subtherapeutic doses.

Drug idiosyncrasy is an abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug. It is not mediated by a humoral or cellular immune response but is reproducible on readministration. Unlike drug intolerance, it is usually due to underlying abnormalities of metabolism, excretion, or bioavailability. A typical example is primaquine-induced hemolytic anemia in glucose-6-phosphate dehydrogenase-deficient individuals.

Drug allergy and hypersensitivity reactions are immunologically mediated responses to pharmacologic agents or pharmaceutical excipients. They occur after a period of sensitization and result in the production of drug-specific antibodies, T cells, or both.

Pseudoallergic reactions, also called anaphylactoid (non-IgE-mediated anaphylaxis) reactions, mimic anaphylactic allergic reactions. Unlike allergic reactions, pseudoallergic reactions do not require a preceding period of sensitization and are not due to the presence of specific IgE antibodies. Pseudoallergic reactions are mediated by a diverse group of agents, such as opiates, colloid volume expanders, basic polypeptide agents (eg, polymyxin B, ACTH), radiocontrast media, excipients (eg, Cremophor-EL), vancomycin, and 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 reaction is immediate and often severe. Because it does not require a preceding period of sensitization, 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 on 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 nonspecific mediator release (eg, hyperosmolar mannitol), but such physical effects are more likely to occur at local tissue sites, such as the nose or bronchi.

### III. CLASSIFICATION OF IMMUNOLOGICALLY MEDIATED DRUG HYPERSENSITIVITY REACTIONS

*Summary Statement 8:* Some drug allergic reactions may be classified by the Gell-Coombs classification paradigm of hypersensitivity (type I: IgE mediated; type II: cytotoxic; type

III: immune complex; type IV: cell mediated), whereas others cannot be classified because of lack of knowledge of their immunopathogenesis or a mixed mechanism. (C)

*Summary Statement 9:* Allergic drug reactions may also be classified according to the predominant organ system involved (eg, cutaneous, hepatic, renal) or according to the temporal relationship to onset of symptoms (immediate, accelerated, delayed). (D)

*Summary Statement 10:* To some extent, the structural characteristics of drugs may permit predictions about the type of hypersensitivity reactions they are likely to cause. (C)

Clinical presentations of drug allergy are often diverse, depending on type(s) of immune responses and target organ specificities). 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 I], cytotoxic [type II], immune complex [type III], and cell mediated [type IV]).<sup>199</sup>

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

*Summary Statement 11:* IgE-mediated reactions may occur after administration of a wide variety of drugs, biologicals, and drug formulation agents, with the most common agents being antibiotics. (C)

Immediate hypersensitivity type I 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, which typically occur within minutes of exposure to the drug. IgE-mediated hypersensitivity reactions may occur after administration of a wide variety of drugs, biologicals, and drug formulation agents. Common causes are large-molecular-mass biologicals and many drugs (eg, penicillin). The most important drug causes of immediate hypersensitivity reactions are antibiotics. Other common drugs that cause such reactions are insulin, enzymes (asparaginase), heterologous antisera (equine antitoxins, antilymphocyte globulin), murine monoclonal antibodies, protamine, and heparin.<sup>100,200-205</sup> Allergic type I reactions have also been reported rarely after exposure to excipients, such as eugenol, carmine, vegetable gums, paraben, sulfites, formaldehyde, polysorbates, and sulfonechloramide.<sup>206-208</sup> In this parameter, we will consider both  $\beta$ -lactam and non- $\beta$ -lactam antibiotics as the major prototypes in this category.

#### B. Cytotoxic Reactions (Gell-Coombs Type II)

*Summary Statement 12:* Cytotoxic reactions are very serious and potentially life-threatening. (C)

*Summary Statement 13:* Immuno-hemolytic anemias have occurred after treatment with quinidine,  $\alpha$ -methyl dopa, and penicillin. (C)

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*Summary Statement 14:* Positive direct and indirect Coombs test results in immunohemolytic anemia may reflect the presence of drug-specific IgG, complement, or an Rh determinant autoantibody. (C)

*Summary Statement 15:* Immune-induced thrombocytopenia may result from treatment with heparin, quinidine, propylthiouracil, gold salts, sulfonamides, vancomycin, and other drugs. (C) Platelet membrane damage is mediated mainly by drug-immune serum complexes, which are adsorbed onto platelet membranes. (C)

*Summary Statement 16:* Immune-mediated granulocytopenia is uncommon but may be induced by cytotoxic antibodies synthesized in response to a variety of drugs. (C)

Cytotoxic (type II) 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. 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.<sup>209-211</sup> In the case of penicillin, circulating antipenicillin antibodies of the immunoglobulin G isotype have been implicated.<sup>209</sup> The condition is rare because it apparently develops only in those individuals capable of synthesizing an atypical variety of IgG antipenicillin 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 test results in this condition also may indicate the presence of complement on the red cell membrane or an autoantibody to an Rh determinant.

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, vancomycin, and the sulfonamides.<sup>212-216</sup> Platelet membrane damage is mediated chiefly by circulating drug-immune serum complexes, which are adsorbed onto platelet membranes.

Granulocytopenia also may be produced by cytotoxic antibodies synthesized in response to such drugs as pyrazolone derivatives, phenothiazines, thiouracils, sulfonamides, and anticonvulsives.<sup>217,218</sup> 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).

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

*Summary Statement 17:* Immune complex (serum sickness) reactions were originally described with use of heterologous antisera, but they may also be caused by some small-molecular-weight drugs and monoclonal antibodies. (C)

*Summary Statement 18:* The chief manifestations of fever, rash, urticaria, lymphadenopathy, and arthralgias typically appear 1 to 3 weeks after starting use of an offending agent. (C)

*Summary Statement 19:* The prognosis for complete recovery from serum sickness is excellent; however, symptoms may last as long as several weeks. Treatment with systemic corticosteroids and histamine<sub>1</sub> receptor antihistamines may be required. (C)

*Summary Statement 20:* Drug-induced immune complex disease may occur after exposure to heterologous proteins (eg, thymoglobulin) or simple drugs (eg, penicillin, procainamide, phenylpropanolamine). (C)

Type III reactions are mediated by immune complexes formed in slight antigen excess. Serum sickness is the prototype for type III reactions. Serum sickness was originally noted when heterologous antisera were used extensively for passive immunization of infectious diseases. However, many small-molecular-weight drugs are also associated with serum sickness-like symptoms. These drugs include penicillin, sulfonamides, thiouracils, and phenytoin. Monoclonal antibody therapies have also been associated with serum sickness-like reactions to several agents, including infliximab, rituximab, omalizumab, and natalizumab. The chief manifestations of fever, rash, urticaria, lymphadenopathy, and arthralgias typically appear 1 to 3 weeks after starting use of an offending drug and begin to subside when the drug and/or its metabolites are completely eliminated from the body.<sup>219</sup> In previously sensitized individuals, the reaction may begin within a few days after administration of the drug. Most of the clinical symptoms are thought to be mediated by IgG and possibly IgM-drug complexes. However, 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 disease. A serum sickness-like reaction also can occur with reactive metabolites (Summary Statement 96). The prognosis for complete recovery is excellent; however, symptoms may last as long as several weeks. Treatment consists of systemic corticosteroids and histamine<sub>1</sub> receptor antihistamines and in some cases nonsteroidal anti-inflammatory drugs (NSAIDs).

Polyclonal antibody therapy (Anti-thymocyte globulin and thymoglobulin) is often used in solid organ transplantation for an immunologic induction and treatment of acute graft rejection.<sup>220</sup> Immune complex-mediated illness (serum sickness) manifested by fever, arthritis, rash, lymphadenopathy, and/or renal failure may occur at a prevalence rate between 7% and 27% of renal transplant patients who receive polyclonal antibody therapy.<sup>221,222</sup> Other drugs that may induce immune complex-mediated serum sickness or vasculitis include penicillin, procainamide, hydralazine, and phenylpropanolamine.<sup>223-225</sup>

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

*Summary Statement 21:* Contact dermatitis produced by topical drugs (such bacitracin, neomycin, glucocorticoste-

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roids, local anesthetics, and antihistamines) and/or excipients contained in topical formulations are due to cell-mediated reactions. (C)

*Summary Statement 22:* It is postulated that Gell-Coombs type IV reactions are also responsible for some delayed cutaneous maculopapular eruptions due to oral antibiotics, such as amoxicillin and sulfonamides. (C)

*Summary Statement 23:* Patch testing at proper concentrations may be successful in detection of suspected contact allergens. (B)

*Summary Statement 24:* After avoidance is instituted, topical and/or systemic corticosteroids may be required for total clearing of the dermatitis (provided that these drugs were not the primary causes). (C)

Delayed hypersensitivity type IV reactions are mediated by cellular immune mechanisms. A recently proposed modification subdivides type IV reactions into 4 categories involving activation and recruitment of monocytes (IVa), eosinophils (IVb), CD4<sup>+</sup> or CD8<sup>+</sup> T cells (IVc), and neutrophils (IVd).<sup>(1)</sup> The classic reaction in this category is contact dermatitis, a condition in which the topical induction and elicitation of sensitization by a drug is entirely limited to the skin. It appears that Gell-Coombs type IV reactions are also responsible for delayed cutaneous eruptions, such as maculopapular exanthems due to antibiotics (eg, amoxicillin and sulfonamides). Delayed hypersensitivity responses may also be systemic, involving lymphoid organs and other tissues throughout the body. Sensitized T cells produce a wide array of proinflammatory cytokines that can ultimately lead to lymphocytic infiltrates, disseminated granulomata, and fibrosis. It has been suggested there is a marked clinicopathological similarity between some late-onset drug reactions and graft vs host reactions that are initiated and maintained by T cells.<sup>226</sup>

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 fewer than 40 allergens produce most cases of contact dermatitis. Among the drugs involved, the most universally accepted offenders are topical formulations of bacitracin, neomycin, glucocorticosteroids, local anesthetics, and antihistamines. Potent excipient topical sensitizers include the parabens, formaldehyde, ethylenediamine, lanolin, and thimerosal.<sup>206</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.

In addition to reactions due to topical application, it is postulated that Gell-Coombs type IV reactions are also responsible for some delayed cutaneous maculopapular eruptions due to oral antibiotics, such as amoxicillin and sulfonamides.<sup>227,228</sup>

## E. Miscellaneous Syndromes

*Summary Statement 25:* Some drugs or classes of drugs are associated with characteristic syndromes that often do not conform to specific Gell-Coombs categories and sometimes are referred to as mixed drug reactions (ie, a mixture of immunologic mechanism). (C)

Some drugs or classes of drugs are associated with characteristic syndromes that often do not conform to specific Gell-Coombs categories. Table 2 highlights the spectrum of drug allergic reactions and syndromes that will be discussed in greater detail in this parameter. Although various specific immune phenomena can often be demonstrated in these syndromes, their roles in the immunopathogenesis of the disease have not been clearly established. Isolation of T-cell clones with characteristic cytokine profiles in some of these reactions suggest that they may ultimately be classified into modified Gell-Coombs categories involving activation and recruitment of monocytes and macrophages (IVa), eosinophils (IVb), cytotoxic T cells (IVc), and neutrophils (IVd).

### 1. Hypersensitivity vasculitis

*Summary Statement 26:* Many drugs, hematopoietic growth factors, cytokines, and interferons are associated with vasculitis of skin and visceral organs. (C)

Many agents, hematopoietic growth factors, cytokines, and the interferons are suspected of causing widespread vascular inflammation of skin and visceral organs.<sup>229,230</sup> Frequently, the vascular changes occur during or at the endstage of drug-induced syndromes of serum sickness or drug fever. Drugs such as hydralazine, antithyroid medications, minocycline, and penicillamine are often associated with antinuclear cytoplasmic antibody- or periantinuclear cytoplasmic antibody-positive vasculitis-like disease.<sup>231</sup> Antineutrophil cytoplasmic antibody-positive vasculitis is also associated with hydralazine-induced systemic lupus erythematosus. Similar findings also apply to propylthiouracil. A Henoch-Schönlein syndrome with cutaneous vasculitis and glomerulonephritis may be induced by carbidopa/levodopa.<sup>232</sup>

### 2. Drug Rash With Eosinophilia and Systemic Symptoms (DRESS) Syndrome

*Summary Statement 27:* The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced, multiorgan inflammatory response that may be life-threatening. First described in conjunction with anticonvulsant drug use, it has since been ascribed to a variety of drugs. (C)

*Summary Statement 28:* Anticonvulsant hypersensitivity syndrome is mainly associated with aromatic anticonvulsant drugs and is related to an inherited deficiency of epoxide hydrolase, an enzyme required for the metabolism of arene

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oxide intermediates produced during hepatic metabolism. (B) Phenytoin, carbamazepine, and phenobarbital are considered cross-reactive, but valproic acid, gabapentin, and lamotrigine are therapeutic alternatives. (C) It is slower in onset than DRESS and presents with skin nodules, plaques, and lymphadenopathy at times confused with lymphoreticular malignant tumors (ie, pseudolymphoma) (B)

The DRESS syndrome is a drug-induced, multiorgan inflammatory response that may be life-threatening. First described in conjunction with anticonvulsant drug use, it has since been ascribed to a variety of drugs. The terms describing this syndrome have varied in the literature, with various terms preferred by some authors, including *phenytoin hypersensitivity syndrome*, *drug hypersensitivity syndrome*, *drug-induced hypersensitivity syndrome*, and *drug-induced delayed multiorgan hypersensitivity syndrome*. Characteristic features of DRESS vary and may include cutaneous eruptions (exanthems, erythema multiforme purpura), fever, eosinophilia (most but not all cases), hepatic dysfunction, renal dysfunction, and lymphadenopathy.<sup>233</sup> Case definitions for DRESS have recently been proposed for a multinational survey.<sup>234</sup> These proposed inclusion criteria include 3 or more of the following: hospitalization, reaction suspected to be drug related, acute rash, temperature higher than 38°C, enlarged lymph nodes at least 2 sites, involvement of at least 1 internal organ, and hematologic abnormalities. Medications implicated in DRESS include anticonvulsants, sulfonamides, allopurinol, minocycline, dapsone, sulfasalazine, abacavir, nevirapine, and hydroxychloroquine. DRESS is atypical from other drug allergic reactions in that the reaction develops later, usually 2 to 8 weeks after therapy is started; symptoms may worsen after the drug therapy is discontinued; and symptoms may persist for weeks or even months after the drug therapy has been discontinued. Human herpesvirus 6 reactivation has been detected in many patients with DRESS within 2 to 3 weeks of the eruption and may be an indicator of more severe disease.<sup>235</sup>

Systemic symptoms of the DRESS syndrome include fever, involvement of internal organs, and an association with previous exposure or infection with a herpesvirus (human herpesvirus 6).<sup>232,236</sup> In addition to anticonvulsants, a variety of drugs have been reported to cause DRESS, including trimethoprim-sulfamethoxazole, minocycline, sulfasalazine, NSAIDs, D-penicillamine, hydrochlorothiazide, cyclosporine, nevirapine, and allopurinol.<sup>237</sup> In the case of allopurinol, toxic intermediates may mediate the abnormal lymphocyte responses.<sup>238</sup> The occurrence of this syndrome after use of valproic acid or gabapentin is rare.

Anticonvulsant hypersensitivity syndrome is life-threatening and may occur after varying (usually longer than DRESS) periods of exposure to anticonvulsive 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 aromatic anticonvulsant drugs. It is characterized by fever, a maculopapular rash, and generalized lymphadenopathy, resembling

the progression of symptoms that occur during a serum sickness-like reaction.<sup>232</sup> Lymphadenopathy mimicking the clinical manifestations of malignant lymphoma (the pseudolymphoma syndrome) was first reported in patients undergoing anticonvulsant therapy. Two presentations are recognized: (1) DRESS 2 to 8 weeks after initiation of therapy and (2) a more insidious onset with skin nodules and plaques, suggesting a pseudolymphoma without systemic symptoms.<sup>232</sup> Hepatitis, nephritis, and leukocytosis with atypical lymphocytes and eosinophils may be part of the syndrome. Facial edema occurs in 25% of the patients. These multiorgan reactions may be induced by phenytoin, carbamazepine, or phenobarbital, and cross-reactivity may occur among all aromatic anticonvulsants that produce toxic arene oxide metabolites

Treatment involves removing the offending agent, and although corticosteroids have been used, their efficacy is unknown. Unlike Stevens-Johnson syndrome or toxic epidermal necrolysis, there is almost never mucosal involvement with DRESS. Unlike serum sickness-like reactions, there is usually no arthralgia. DRESS is atypical of most all other drug reactions in that symptoms and organ involvement can continue to progress after use of the offending agent has been discontinued. Furthermore, symptoms may persist for many months after drug therapy discontinuation. Relapses have occurred after tapering of corticosteroids. There are limited data on the use of intravenous immunoglobulin and other immunomodulatory agents in resistant cases.<sup>239</sup>

### 3. Pulmonary Drug Hypersensitivity

*Summary Statement 29:* Pulmonary manifestations of allergic drug reactions include anaphylaxis, lupuslike reactions, alveolar or interstitial pneumonitis, noncardiogenic pulmonary edema, and granulomatous vasculitis (ie, Churg-Strauss syndrome). Specific drugs are associated with different types of pulmonary reactions, such as bleomycin-induced fibrosis. (C)

Pulmonary manifestations of allergic drug reactions include anaphylaxis, lupuslike reactions, alveolar or interstitial pneumonitis, edema, granulomatosis, and fibrosis.<sup>240</sup> Acute pneumonitis with fever, rash, and eosinophilia occurs after treatment with nitrofurantoin, NSAIDs, and sulfasalazine. If the drugs are not eliminated properly, these lesions may progress to a chronic course with interstitial fibrosis. Hypersensitivity pneumonitis may occur in association with NSAID treatment. Biopsy-proven eosinophilic pneumonia may occur after use of sulfonamides, penicillin, and para-aminosalicylic acid. Patchy pneumonitis, pleuritis, and pleural effusion may appear during various drug-induced lupus syndromes.<sup>241</sup> Whether 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.<sup>240</sup> These le-

Table 4. Drug-Induced Lupus Erythematosus (DILE)

	Systemic DILE	Cutaneous DILE
Incidence	Rare	More frequent cause of subcutaneous lupus erythematosus
Drugs Implicated	Hydralazine, procainamide, isoniazid, methyldopa, quinidine, minocycline, chlorpromazine	Hydrochlorothiazide, calcium channel blockers, ACE inhibitors, systemic antifungal agents
Onset of symptoms	Gradual escalation of symptoms over months	Onset of symptoms within 4-8 weeks
Systemic Symptoms	Arthralgias and myalgias frequent	No systemic symptoms
Cutaneous symptoms	Photosensitivity, purpura, erythema nodosum more frequent	Photosensitive erythema, scaly annular plaques
Serologic testing	Antihistone antibodies >90% overall Anti-Ro/SSA and/or anti-La/SSB usually negative	Antihistone antibodies <25% Anti-Ro/SSA and/or anti-La/SSB frequently positive

Abbreviation: ACE, angiotensin-converting enzyme.

sions 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 chronic organizing pneumonia), the pulmonary-renal syndrome associated with D-penicillamine, and several granulomatous vasculitides.<sup>240,242</sup>

#### 4. Drug-Induced Lupus

*Summary Statement 30:* Drug-induced lupus erythematosus (DILE) can have systemic forms and predominantly cutaneous forms. Procainamide and hydralazine are the most frequently implicated drugs for systemic DILE, and antihistone antibodies are present in more than 90% of patients but occur less commonly with minocycline, propylthiouracil, and statins. (C)

*Summary Statement 31:* Drugs most commonly associated with cutaneous DILE include hydrochlorothiazide, calcium channel blockers, angiotensin-converting enzyme inhibitors, and systemic antifungal agents. Anti-Ro and anti-SSA antibodies are usually present, where antihistone antibodies are much less frequent. (C)

DILE is thought to represent up to 10% of systemic lupus erythematosus cases.<sup>243</sup> Similar to idiopathic lupus, DILE can have systemic forms and predominantly cutaneous forms (Table 4). Systemic DILE usually occurs after years of exposure to the offending drug and resolves within weeks to months after withdrawal of the causative agent. Procainamide and hydralazine are the most frequently implicated drugs, but causal evidence is also convincing for isoniazid, methyldopa, quinidine, minocycline, and chlorpromazine.<sup>244</sup> The most frequent signs and symptoms of systemic DILE are arthralgias, myalgias, fever, malaise, and weight loss. Hypocomplementemia and antibodies to double-stranded DNA (dsDNA) are rare, whereas antihistone antibodies are present in more than 90% of patients with DILE overall but occur less frequently with minocycline, propylthiouracil, and statins.<sup>244</sup> DILE related to anti-tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) drugs demonstrate several differences from classic DILE, including more frequent rash (>70%), antibodies to dsDNA (90%), and hypocomplementemia (>50%) and less frequent antihistone antibodies.<sup>245</sup>

Cutaneous DILE differs from systemic DILE in respect to several features. Drugs most commonly associated with cutaneous DILE include hydrochlorothiazide, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and systemic antifungal agents.<sup>246</sup> Anti-Ro and anti-SSA antibodies are usually present, whereas antihistone antibodies are much less frequent.<sup>244</sup> The onset of cutaneous DILE is much faster than systemic DILE, with disease being triggered typically in 4 to 8 weeks.

#### 5. Drug-Induced Granulomatous Disease With or Without Vasculitis

*Summary Statement 32:* The recognition of immunologically mediated, drug-induced granulomatous disease with or without vasculitis has increased in recent years. (C)

Drug-induced, antineutrophil cytoplasmic antibody-positive patients may present either as the Churg-Strauss Syndrome (CSS) or Wegener granulomatosis (WG), both of which are classified as systemic granulomatous vasculitides.<sup>247,248</sup> Case reports have documented their occurrence in patients receiving various drugs (cocaine, estrogens, acetaminophen, macrolide antibiotics, antithyroid drugs, and leukotriene-modifying agents).<sup>249-253</sup> Antithyroid drugs (eg, propylthiouracil) are more likely to induce WG and a lupuslike syndrome, but a few instances of CSS have been reported.<sup>252</sup> Several published investigations have attributed a higher prevalence of CSS in association with antiasthma drugs, particularly the use of antileukotrienes.<sup>254-256</sup> This has been postulated to occur because of the oral steroid sparing effect of these agents with subsequent unmasking of quiescent CSS as steroids are tapered, although CSS has occurred in some antileukotriene-treated patients who did not receive prior glucocorticosteroids.<sup>251</sup> However, given the inconclusive and contradictory reports on this subject, no direct causal effect of leukotriene modifiers has been established and further research is needed.<sup>257</sup>

#### 6. Immunologic Hepatitis

*Summary Statement 33:* Immunologic hepatitis may occur after sensitization to para-aminosalicylic acid, sulfonamides, and phenothiazines. (C)

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There is strong circumstantial evidence that immunologic hepatitis occurs after sensitization to para-aminosalicylic acid, sulfonamides, and phenothiazines.<sup>258</sup> Cholestatic jaundice is a prominent feature of liver disease induced by phenothiazine, amoxicillin/clavuronic acid, and ranitidine.<sup>259-261</sup> Less well defined are possible immunologic aberrations associated with hepatocellular changes occurring after halothane, anticonvulsives, erythromycin, indomethacin, and isoniazid.

Drugs such as oxyphenisatin, methyl dopa, nitrofurantoin, diclofenac, interferon, pernoline, minocycline, and atorvastatin may induce hepatocellular damage that mimics autoimmune hepatitis.<sup>262</sup> Herbal agents, such as black cohosh and dai-saiko-to, may trigger autoimmune hepatitis. Whether these drugs or herbs unmask or induce autoimmune hepatitis or cause drug-induced hepatitis with accompanying autoimmune features is unknown. There are no generally available diagnostic methods to distinguish between hepatic immunologic and toxic reactions due to drugs, such as itraconazole.

## 7. Blistering Disorders

*Summary Statement 34:* Erythema multiforme minor is a cell-mediated hypersensitivity reaction associated with viruses, other infectious agents, and drugs. It manifests as pleomorphic cutaneous eruptions, with target lesions being most characteristic. (C)

*Summary Statement 35:* There is no consensus on the distinction between erythema multiforme major and Stevens-Johnson syndrome. These disorders involve mucosal surfaces and the skin. (D)

*Summary Statement 36:* Use of systemic corticosteroids for treatment of erythema multiforme major or Stevens-Johnson syndrome is controversial. (D)

*Summary Statement 37:* Toxic epidermal necrolysis (ie, Lyell syndrome) is distinguished from Stevens-Johnson syndrome by the extent of epidermal detachment. (D)

*Summary Statement 38:* Systemic corticosteroids are associated with increased mortality when used for the management of advanced toxic epidermal necrolysis (C). Treatment with high-dose intravenous immunoglobulin is controversial. (D)

*Summary Statement 39:* Toxic epidermal necrolysis should be managed in a burn unit. (D)

### a. Erythema Multiforme Minor

Erythema multiforme minor appears to be a cell-mediated hypersensitivity reaction associated with viruses, other infectious agents, and drugs. It is manifested by pleomorphic cutaneous eruptions; at times bullous and target lesions are also characteristic. A specific form of erythema multiforme minor may develop in the radiation field of oncologic patients receiving phenytoin for prophylaxis of seizures caused by brain metastases (EMPACT: EM associated with Phenytoin and Cranial Radiation Therapy).<sup>263</sup> If a drug cause is suspected, use of the drug should be stopped immediately and the addition of glucocorticosteroids may be necessary. Anti-

histamines may assist with treatment of pruritus. Early treatment of erythema multiforme minor with systemic corticosteroids may prevent progression to the more serious erythema multiforme major/Stevens-Johnson syndrome.

### b. Erythema Multiforme Major/Stevens-Johnson Syndrome

Drugs are an important cause of the erythema multiforme major/Stevens-Johnson syndrome (SJS) and 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 oxicam derivatives, whereas drugs in the moderate risk category included quinolones, carbamazepine, phenytoin, valproic acid, and glucocorticosteroids.<sup>264</sup> Rarely, vancomycin may induce several forms of bullous skin disease. One of these is subdermal, blistering disorder characterized by IgA deposition beneath the basement membrane. Biopsy with direct immunofluorescence is required to distinguish this reaction from the SJS and TEN, which can also be induced by this drug. As described under the Physical Examination section (section V), target and bullous lesions primarily involving the extremities and mucous membranes are characteristic of erythema multiforme major, whereas the features of SJS are confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than 1 mucosal surface, that are accompanied by a high temperature 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, use of the suspected drug should be stopped immediately. The use of glucocorticosteroid therapy is controversial.<sup>265-267</sup> If it is started, it should probably be initiated early in the disease and very high doses should be used.<sup>268</sup> However, if this treatment is started too late in the disease (ie, 3 to 4 days after onset), it is possible that TEN could supervene, in which case systemic glucocorticosteroids are contraindicated.<sup>265,269</sup>

### c. Toxic Epidermal Necrolysis

SJS and TEN are probably part of a single disease spectrum. According to a commonly used classification scheme, if epidermal detachment is less than 10%, the disease is SJS, but when epidermal detachment reaches 30% or more, the diagnosis is TEN.<sup>270</sup> In cases with detachment of 10% to 30% of the epidermis, the 2 syndromes are considered overlapping. TEN 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>265</sup> There is a significant risk of infection, and mortality rates as high as 50% have been reported.<sup>271</sup> TEN should be distinguished from the scalded skin syndrome, a disorder caused by staphylococcal bacterial toxin and characterized by the massive

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skin cleavage and separation in the uppermost epidermis. A number of open-label, retrospective, and prospective noncontrolled studies have demonstrated improved outcomes (such as lower mortality rates, shorter time to interruption of lesion progression, shorter time to complete reepithelialization) in patients with TEN treated with high-dose intravenous immunoglobulins (IVIGs).<sup>272-276</sup> Other studies using similar methods found no beneficial effects of IVIG on TEN.<sup>277-279</sup> The typical dose of IVIG used in these studies was approximately 0.5 to 1 g/kg per day for 3 to 4 days. The mechanism of action of IVIG is believed to be inhibition of Fas-Fas ligand associated apoptosis, which has been found to be extensive in keratinocytes of patients with TEN.<sup>280</sup> There are limited data to suggest that anti-TNF- $\alpha$  treatment is beneficial in TEN.<sup>281,282</sup>

## 8. Serum Sickness-Like Reactions Associated With Specific Cephalosporins

*Summary Statement 40:* Serum sickness-like reactions caused by cephalosporins (especially cefaclor) usually are due to altered metabolism of the drug, resulting in reactive intermediates. (B)

Cefaclor and to a lesser extent 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>283-286</sup> Serum-sickness-like reactions to cefaclor appear to result from altered metabolism of the parent drug, resulting in toxic reactive intermediate compounds.<sup>283</sup> This altered metabolism can often be documented in a parent of the patient.<sup>283</sup> Anecdotally, affected patients later have tolerated other cephalosporins. In vitro tests for toxic metabolites have confirmed a lack of cross-reactivity between cefaclor and other cephalosporins.<sup>287</sup> Therefore, patients with serum sickness-like reactions to cefaclor and cefprozil may not need to avoid other cephalosporins.

## 9. Immunologic Nephropathy

*Summary Statement 41:* Immunologically mediated nephropathies may present as interstitial nephritis (such as with methicillin) or as membranous glomerulonephritis (eg, gold, penicillamine, and allopurinol). (C)

The major example of drug-induced immunologic nephropathy is an interstitial nephritis induced by large doses of benzylpenicillin, methicillin, or sulfonamides.<sup>288,289</sup> In addition to symptoms of tubular dysfunction, these patients demonstrate fever, rash, eosinophilia (especially in the urine), and high levels of total IgE, which revert to normal on discontinuation of use of the offending drug.<sup>290</sup> The predominant lesion of the nephrotic syndrome induced by gold, penicillamine, and allopurinol is a membranous glomerulonephritis.<sup>288,291</sup> An immunologic basis of this lesion is suggested by deposition of IgG, IgM, and C3 in glomerular lesions.<sup>292</sup> In the rare pulmonary-renal syndrome induced by penicillamine, "lumpy" intraglomerular deposits of complement and/or im-

munoglobulins are commonly observed.<sup>242</sup> Renal vasculitis has also been reported.<sup>293,294</sup>

## F. Other Classification Systems for Drug Allergy

*Summary Statement 42:* In addition to Gell-Coombs hypersensitivity reactions, there are a number of other mechanistic and clinical classifications for drug allergy. (C)

*Summary Statement 43:* The p-i concept (pharmacologic interaction with immune receptors) is a recently proposed addition to drug hypersensitivity classification in which a drug binds noncovalently to a T-cell receptor, which may lead to an immune response via interaction with a major histocompatibility complex receptor. (C)

*Summary Statement 44:* From a clinical standpoint, the most practical method of classifying drug reactions is by predilection for various tissue and organ systems. (D)

*Summary Statement 45:* The structural characteristics of drugs and biological products may permit predictions about what type of hypersensitivity reactions to expect from certain classes of therapeutic substances. (C)

In addition to the Gell-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, such as 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 p-i concept (pharmacologic interaction with immune receptors) is a recently proposed addition to drug hypersensitivity classification. In this scheme, a drug binds noncovalently to a T-cell receptor, which may lead to an immune response via interaction with a major histocompatibility complex receptor. In this scenario, no sensitization is required because there is direct stimulation of memory and effector T cells, analogous to the concept of superantigens.<sup>2,3</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. The pulmonary system is also recognized as a favorite site for certain drug hypersensitivity reactions. Other individual tissue responses to drugs include cytotoxic effects on 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 hour to 3 days), or delayed (beyond 3 days).<sup>295</sup>

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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. 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 blood vessels. Although immune responses induced by carbohydrate agents are infrequent, anaphylaxis has been described after topical exposure to carboxymethylcellulose.<sup>296</sup> Any single or mixed variety of immune responses may occur after exposure to low-molecular-mass ( $\leq 1,000$ Da) inorganic or organic medicinal chemicals. The immunogenic potential of such drugs is often determined by 1 or more reactive end products or metabolites, which haptenate with various body proteins. The parent compound itself is not immunogenic because of its small size and inability 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 of metabolic enzymes may be at higher risk for allergic and autoimmune disorders induced by drugs.<sup>283,297,298</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.

#### IV. RISK FACTORS

*Summary Statement 46:* The most important risk factors for drug hypersensitivity may be related to the chemical property and molecular weight of drugs. (C)

*Summary Statement 47:* Other drug-specific risk factors for drug hypersensitivity include the dose, route of administration, duration of treatment, repetitive exposure to the drug, and concurrent illnesses (eg, Epstein-Barr virus infection and amoxicillin rash). (C)

*Summary Statement 48:* Host risk factors for drug hypersensitivity include age, sex, atopy, underlying diseases (such as lupus, erythematous, and human immunodeficiency virus) and specific genetic polymorphisms. (C)

The chemical properties, amount and duration of exposure to the drug, and host factors may all interact in the development of drug allergy. Large-molecular-weight 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>299,300</sup>

Parenteral and cutaneous administrations of a drug enhance the possibility of sensitization, whereas the oral route of administration may be safer.<sup>301</sup> Single doses of a prophylactic antibiotic are less likely to sensitize compared with high-dose prolonged parenteral administration of the same drug. Frequent repetitive courses of therapy are also more likely to sensitize, which accounts for the high prevalence of sensitization in patients with cystic fibrosis.

Host factors and concurrent medical illnesses are significant risk factors. In the case of penicillin, allergic reactions appear to occur less frequently in children and in elderly patients.<sup>302</sup> Immaturity and senescence of the immune response may account for these observations. Older age was found to be a risk factor for development of ADRs in hospitalized patients,<sup>303</sup> and this may be related to declining cognitive function.<sup>304</sup> In a prospective study, women were shown to have a 35% higher incidence of adverse cutaneous reactions to drugs than men.<sup>305</sup> In another study, the odds ratio for women developing reactions to radiocontrast media was 20-fold greater than for men.<sup>122</sup>

A subset of patients shows a marked tendency to react to clinically unrelated drugs, especially antibiotics.<sup>27,306-308</sup> These reactions encompass urticaria, rashes, serum sickness-like drug reactions, angioedema, anaphylaxis, and SJS. Compared with monosensitive patients, many of these patients show evidence of circulating histamine-releasing factors, as assessed by autologous serum skin tests.<sup>309</sup> It has also been suggested that previous intolerance to NSAIDs might be a risk factor for some patients with this condition.<sup>310</sup> Allergic reactions to multiple structurally unrelated antibiotics appear to occur more often in women.<sup>308</sup> There are limited data to suggest a familial component to drug allergy, but the studies are limited by a reliance on patient history (which is known to be a poor predictor of drug allergy) and by lack of confirmatory testing or provocative challenges.<sup>311</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>312</sup> Allergic reactions to abacavir have been associated with the presence of HLA B 5701.<sup>97,98</sup> Patients with systemic lupus erythematous 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.<sup>313,314</sup> Patients with systemic mastocytosis appear to be at increased risk of pseudoallergic reactions to narcotics and vancomycin. The presence of an atopic diathesis (allergic rhinitis, allergic asthma, and/or atopic dermatitis) predisposes patients to a higher rate of allergic reactions to proteins (eg, latex) but not to low-molecular-weight agents.<sup>315-317</sup> Paradoxically, atopic patients appear to have a greater risk of non-IgE-mediated, pseudoallergic reactions induced by radiocontrast media.<sup>123</sup> Asthma appears to be associated with a substantially increased risk of serious allergic reactions (including certain

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causes of anaphylaxis) once an IgE antibody response to any drug has developed.<sup>301,302</sup>

## V. CLINICAL EVALUATION AND DIAGNOSIS OF DRUG ALLERGY

### A. History

*Summary Statement 49:* The history should focus on previous and current drug use and the temporal sequence of events between initiation of therapy and onset of symptoms. (C)

The first question facing the physician in the evaluation of a patient with a suspected ADR is whether the clinical problem is drug related. The subsequent clinical evaluation and diagnosis of unpredictable (type B) drug reactions is based on a number of clinical criteria:

- 1) The symptoms and physical findings are compatible with an unpredictable (type B) drug reaction;
- 2) There is a temporal relationship between administration of the drug and an adverse event. Patients may develop drug reactions after discontinuation of use of the drug.
- 3) The class and chemical structure of the drug have been associated with unpredictable reactions;
- 4) In cases of drug allergic reactions, the patient has previously been exposed to the drug on 1 or more occasions (with the possible exception of serum sickness–like reactions). For infants, the prior exposure may have taken place either in utero or via breast milk.
- 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 test results and/or laboratory findings (if available) are compatible with drug allergic reactions.

For most drug reactions, these questions are answered on the basis of information derived from the history and physical examination. A careful history of previous and current drug use, focusing particularly on the temporal sequence of events between initiation of therapy and onset of symptoms is probably the most useful information for the diagnosis of an allergic drug reaction. In this regard, specific knowledge about the pharmacology 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 discussed, general and specific host risk factors should also be noted in the medical history.

### B. Physical Examination

*Summary Statement 50:* Physical examination should include all systems that could possibly account for the clinical presentation. (C)

*Summary Statement 51:* Cutaneous manifestations are the most common presentation for drug allergic reactions. Characterization of cutaneous lesions is important in regard to determining the cause, further diagnostic tests, and management decisions. (C)

*Summary Statement 52:* Numerous cutaneous reaction patterns have been reported in drug allergy, including exan-

thems, urticaria, angioedema, acne, bullous eruptions, fixed drug eruptions, erythema multiforme, lupus erythematosus, photosensitivity, psoriasis, purpura, vasculitis, pruritus, and life-threatening cutaneous reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and drug rash with eosinophilia and systemic symptoms (DRESS). (C)

Because drug reactions may involve virtually any organ system, a careful physical examination is recommended. Cutaneous manifestations are the most common presentation for drug allergic reactions. Characterization of cutaneous lesions is important in regard to determining the cause, further diagnostic tests, and management decisions. Numerous cutaneous reaction patterns have been reported in drug allergy, including exanthems, urticaria, angioedema, acne, bullous eruptions, fixed drug eruptions, erythema multiforme, lupus erythematosus, photosensitivity, psoriasis, purpura, vasculitis, pruritus, and life-threatening cutaneous reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and drug rash with eosinophilia and systemic symptoms.<sup>4</sup>

The most common cutaneous manifestation of drug allergic reactions is a generalized exanthem (maculopapular eruption). These lesions are pruritic, often beginning as macules that can evolve into papules and eventually may coalesce into plaques. Drug-induced exanthems typically involve the trunk and spread outward to the limbs in a bilateral symmetric pattern. Many drug-induced exanthems are manifestations of delayed-type hypersensitivity. The development of a drug exanthem typically evolves after several days of taking the offending drug. With resolution of an exanthem, scaling may occur. This should be distinguished from the type of epidermal detachment seen in severe cutaneous reactions that occurs early in the reaction. Drug-induced exanthems do not evolve into anaphylactic reactions because they are not IgE-mediated reactions. Many drugs are capable of causing exanthems; however, certain medications, such as allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides, are some of the more frequent culprit drugs.<sup>318</sup> Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) specifically refers to the distinctive, sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area along with involvement of at least 1 other intertriginous/flexural region.<sup>319</sup> This specific pattern of exanthem has been previously referred to as baboon syndrome; however, the term *SDRIFE* has been proposed to distinguish this reaction from topical contact allergens.

Fixed drug eruptions recur at the same skin or mucosal site on reintroduction of the causative drug. Typical fixed drug eruptions present as round or oval, sharply demarcated, red to livid, slightly elevated plaques, ranging from a few millimeters to several centimeters in diameter.<sup>320</sup> They may also present as vesicles, and mucosal lesions are usually bullous. Fixed drug eruptions have a predilection for the lips, hands, and genitalia (especially in men). Fixed drug eruptions can

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occur with a number of medications, including tetracycline, NSAIDs, and carbamazepine.

Urticaria and angioedema are the most common manifestations of IgE-mediated drug allergy. However, it is important to recognize that non-IgE-mediated drug allergic reactions can manifest with urticaria and angioedema too. Urticaria is the most common manifestation of serum sickness; however, the presence of maculopapular lesions of the sides of the fingers and toes or a serpiginous distribution of such lesions along lateral aspects of both soles may be more specific for serum sickness. Angioedema due to ACE inhibitors is likely a bradykinin-mediated manifestation of angioedema.

Photoallergic reactions may present with eczematous eruptions in a photodistribution on the face, “V” area of the neck, dorsa of hands, and arms, with sparing of the scalp, submental, and periorbital areas. Phototoxic reactions typically present with erythroderma within minutes to hours of sunlight exposure but may present with vesicles with severe reactions. Drug-induced cutaneous lupus may also present with eruptions in a photodistribution, typically with erythema or scaly, annular plaques.

Lichenoid drug eruptions may resemble lichen planus and present with violaceous, polygonal papules. Medications reported to cause lichenoid drug eruptions include ACE inhibitors, furosemide, NSAIDs, proton pump inhibitors, and imatinib.

Palmar-plantar erythrodysesthesia (also known as hand-foot syndrome) presents typically 2 to 12 days after chemotherapy with edema and erythema of the palms and soles and may progress to blistering, ulceration, or necrosis.<sup>321</sup> Doxorubicin, especially the pegylated liposomal form, is a common culprit.

Several cutaneous drug reactions may present with pustules. Acne can occur with glucocorticoids, androgens, lithium, phenytoin, and isoniazid and is common with the immunosuppressant sirolimus.<sup>322</sup> Acute generalized eczematous pustulosis (AGEP) is a rare type of drug eruption that begins with erythema or edema in the intertriginous areas or face. Afterward, fine nonfollicular sterile pustules develop. Fever, neutrophilia, and, in one-third of cases, eosinophilia may also be present.<sup>323</sup> Atypical target lesions, blisters, and oral mucosal involvement are uncommon but may be confused with SJS. Implicated drugs include antibiotics and calcium channel blockers. AGEP is T-cell-mediated drug reaction with drug-specific CXCL8 T cells secreting interleukin 8, resulting in a neutrophilic dermatitis.<sup>324</sup> Finally, drug-induced Sweet syndrome may present with fever, painful nodules, pustules, and plaques and a neutrophilic dermatosis. Granulocyte colony-stimulating factor, sulfonamide antibiotics, and minocycline may all cause drug-induced Sweet syndrome.

Drug allergic reactions may also present with vesicles. Drug-induced pemphigus is most often caused by drugs containing a thiol group (eg, captopril, penicillamine) and presents with flaccid blisters. Drug-induced bullous pemphigoid presents with tense bullae on the extremities, trunk, and occasionally mucous membranes. ACE inhibitors, furo-

semide, penicillin, and sulfasalazine are some of the causative drugs implicated in drug-induced bullous pemphigoid. A similar drug eruption with tense bullae is linear IgA bullous disease, with vancomycin being the most commonly incriminated drug. Vancomycin-induced linear IgA bullous disease is not dose dependent, and the severity does not appear to correlate with serum vancomycin levels.<sup>325</sup>

Purpura and petechiae are often cutaneous stigmata of vasculitis, which can be drug induced. Leukocytoclastic vasculitis may be drug induced by many drugs, including antibiotics, NSAIDs, and diuretics.

Erythema multiforme is a polymorphous maculopapular lesion that spreads peripherally and clears centrally to form an annular pattern known as a “target” lesion. This consists of 3 zones: an erythematous central papule that may blister, an edematous middle ring, and an erythematous outer ring.

In an exaggerated form, erythema multiforme may progress to the development of blisters and progressive involvement of the mucous membranes. Although this symptom complex is termed erythema multiforme major and is often used synonymously with the SJS, some clinicians specify that the 2 conditions have distinguishing features. Target lesions, particularly on the extremities, are still present in erythema multiforme major, whereas widespread blistering purpuric macules of the face, trunk, and proximal extremities are characteristic of SJS.<sup>265</sup> At this stage, more than 1 mucosal site is involved and there are progressive constitutional symptoms. The clinical presentation of SJS may evolve into TEN, a severe drug-induced skin disease in which apoptotic, epidermal cell death results in the separation of large areas of skin at the dermoepidermal junction, producing the appearance of scalded skin.<sup>265</sup> SJS and TEN are probably part of a single disease spectrum, with epidermal detachment less than 10% in SJS, greater than 30% in TEN, and 10% to 30% detachment is considered an overlap syndrome.

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 and erythematous epidermis. Systemic manifestations, such as chills and fever, are common.

Acute life-threatening drug reactions can involve the upper and lower respiratory tracts and the cardiovascular system. For a more detailed discussion of signs and symptoms of anaphylaxis, see the Anaphylaxis Practice Parameter.<sup>326</sup> Drug reactions may present as an isolated fever, occasionally with a temperature in excess of 104°F. In addition, drug reactions may cause a wide array of physical abnormalities, including mucous membrane lesions, lymphadenopathy, hepatosplenomegaly, pleuropneumopathic abnormalities, and joint tenderness or swelling. With any drug reaction associated with the loss of skin integrity, secondary infection should be considered.

### C. General Clinical Tests

*Summary Statement 53:* Possible laboratory tests might include but are not limited to a chest x-ray examination,

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electrocardiography, a complete blood cell count with differential, sedimentation rate or C-reactive protein, autoantibody tests, and specific immunologic tests. (C)

Routine laboratory evaluation appropriate to the clinical setting may be useful for the evaluation of a patient with suspected drug reaction, depending on the history and physical examination findings (see below). A complete blood cell count with a differential cell count and a total platelet count may help to exclude the possibility of cytotoxic reactions. Eosinophilia may be observed as an accompaniment of drug fever, immune complex syndromes, eosinophilic pneumonias, and the Churg-Strauss Syndrome, although most drug reactions are not associated with eosinophilia. If renal involvement is suspected (eg, serum sickness, vasculitis), urinalysis should be considered, looking for the presence of proteinuria, casts, and eosinophils. The presence of urine eosinophils combined with an increase in total IgE may suggest the presence of interstitial nephritis.<sup>290</sup>

The following tests may be helpful for identifying inflammation associated with drug-induced vasculitis. These include measurement of a sedimentation rate (or C-reactive protein), complement tests (looking for evidence of consumption indicated by reduced total complement or complement components) and several autoantibody tests (antinuclear antibody [ANA], antinuclear cytoplasmic antibody [c-ANCA], and perinuclear cytoplasmic antibody [p-ANCA]). A positive ANA result may point to the diagnosis of the drug-induced lupus syndrome induced by drugs such as procainamide and hydralazine. Abnormalities in c-ANCA or p-ANCA frequently occur in drug-induced systemic vasculitides and the Churg-Strauss syndrome.<sup>229</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 test results are helpful, but negative test results do not exclude the possibility of immune complex disease.

A retrospective diagnosis of anaphylaxis may be made by detecting an increase in serum total tryptase levels above baseline or in serum mature tryptase (also known as  $\beta$ -tryptase), which peak 0.5 to 2 hours after drug administration and then decrease with a half-life of approximately 2 hours. Practically, an elevated level may be detected in the serum for 2 to 4 hours (or more) after the reaction, depending on the magnitude of hypotension, which correlates with the peak elevation of serum mature or total tryptase. An elevated 24-hour urine histamine and/or *N*-methylhistamine also may be detected as a clinical indicator of anaphylaxis.<sup>327</sup>

#### D. Specific Tests

*Summary Statement 54:* The most useful test for detecting IgE-mediated drug reactions caused by penicillin and many

large-molecular-weight biologicals is immediate hypersensitivity skin testing. (B)

*Summary Statement 55:* Specialized immunologic tests are sometimes able to confirm the immunologic basis of drug-induced cytotoxic reactions. (B)

*Summary Statement 56:* Drug patch testing may be useful for certain types of cutaneous drug reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions, but generally is not helpful for Stevens-Johnson syndrome or urticarial eruptions. The lack of standardization of reagent concentrations may limit the clinical usefulness of drug patch testing. (B)

*Summary Statement 57:* Lymphocyte proliferation assays may have utility as retrospective indicators of cell-mediated drug reactions, but their positive and negative predictive values have not been determined and they are not available in most medical centers. (C)

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 immunopathological sequelae 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 immunopathological 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 having a type I reaction if the drug is administered. This is helpful in the case of high-molecular-weight agents.<sup>328</sup> Penicillin is the only low-molecular-weight agent for which validated testing has been documented (see section VII on penicillin testing for details).<sup>17,328</sup> 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 assessing immune responses to most small-molecular-weight drug chemicals.

The presence of other isotypic antibody classes (eg, drug-specific IgG4) or cell-mediated immunity often is poorly correlated with immunopathological mechanisms because 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 high-molecular-weight and several low-molecular-weight agents may be useful for confirming the diagnosis and prediction of future IgE-mediated reactions, such as anaphylaxis and urticaria.<sup>17,317,328</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

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control test result, dermatographism or generalized eczema), specific IgE in vitro assays (eg, RAST, Immunocap, Immulonite) are available, although most are not adequately standardized. In the case of small-molecular-weight drugs, validated and reliable skin test reagents are only available for penicillin. Relatively few studies with small numbers of patients have evaluated the specificity and sensitivity of third-generation assays for detection of penicillin specific IgE in vitro.<sup>5,6</sup> These studies demonstrate relatively high specificity (97%-100%) but lower sensitivity (29%-68%) for penicillin specific IgE. Therefore, although a positive in vitro test result for penicillin specific IgE is highly predictive of penicillin allergy, a negative in vitro test result does not adequately exclude penicillin allergy. 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 sections V and VII. 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 present in drug-induced hemolytic anemia. This may reflect the presence of complement and/or a drug on the red cell membrane or an Rh determinant autoantibody (eg, as occurs with  $\alpha$ -methyl dopa). Sensitive drug-specific assays for IgG and IgM antibodies have been developed. Although these may be useful as diagnostic adjuncts, elevated levels can occur in individuals who receive the drug and do not experience a clinical reaction.<sup>329</sup> Complement-dependent assays to detect drug-specific cytotoxic antibodies have also been reported. However, by and large, these tests are only available in specific research laboratories and therefore are not clinically applicable for most drugs.

The diagnosis of contact dermatitis can be verified by patch testing. The details of this technique are discussed in greater detail in the diagnostic testing practice parameter.<sup>330</sup> In recent years there have been reports concerning the diagnostic utility of patch tests with systemically administered drugs in non-IgE-mediated cutaneous drug reactions.<sup>331,332</sup> Drug patch testing may be useful for certain types of cutaneous reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions,<sup>12-14</sup> but generally is not helpful for SJS or urticarial eruptions.<sup>12,15</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 lack of standardization of reagent concentrations may limit the clinical usefulness of this procedure; however, recommendations for a standardized approach to drug patch tests have been proposed.<sup>333</sup>

The lymphocyte transformation test has been studied as an in vitro correlate of drug-induced cellular reactions.<sup>334</sup> This is used primarily as a retrospective test and is not clinically available in most medical centers. There is considerable dis-

agreement among investigators about the value of this assay in evaluating drug allergies because neither its positive nor negative predictive value has been systematically investigated. The lymphocyte transformation test has recently become commercially available for selected drugs, but there are no published studies using these assays, either alone or in comparison with previous independent assays. One potential advantage of the lymphocyte transformation test for some patients is that it is possible to obtain in vitro evidence of lymphocyte transformation by the parent drug itself and liver microsomal products of the drug, thereby bypassing the need for precise knowledge of metabolic determinants.<sup>334,335</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<sup>+</sup> and CD8<sup>+</sup> T-cell responses and drug specific T<sub>H</sub>1 and/or T<sub>H</sub>2 responses.<sup>227,228,336-338</sup> The basophil activation test is a recently described method of evaluating expression of CD63 on basophils after stimulation with an allergen.<sup>7</sup> There are limited data using this method to evaluate patients with possible allergies to  $\beta$ -lactam antibiotics and NSAIDs.<sup>8-10</sup> Further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool.

## E. Tissue Diagnosis

*Summary Statement 58:* In complex cases where multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy may be useful in suggesting a drug-induced eruption. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy may not definitively exclude alternative causes. (C)

Occasionally biopsies of involved organs may define specific histopathological lesions. Skin biopsies may also be of value in the diagnosis and management of drug allergic reactions. However, they usually are not helpful for implicating a particular drug. In complex cases where multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy may be useful in suggesting a drug-induced eruption. Skin biopsies are useful in differentiating vasculitis, bullous diseases, and contact dermatitis.<sup>265</sup> However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy may not definitively exclude alternative causes.<sup>16</sup> Furthermore, features suggestive of drug exanthems, such as interface dermatitis with vacuolar alteration of keratinocytes, foci of spongiosis, and tissue eosinophilia, are not specific and may be seen with other cutaneous diseases.

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>292</sup> In interstitial nephritis, fluorescent antibody studies of renal biopsy specimens reveal that implicated drugs bind to tubular basement membranes and may induce an immune response to bound antigen or the modified basement membrane protein. Lung

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biopsies also may be helpful for identifying conditions such as interstitial fibrosis and eosinophilia.

## VI. MANAGEMENT AND PREVENTION OF DRUG HYPERSENSITIVITY REACTIONS

### A. General

*Summary Statement 59:* Ideally ADRs should be prevented. Steps to prevent allergic drug reactions include (1) a careful history to determine host risk factors, (2) avoidance of cross-reactive drugs, (3) use of predictive tests when available, (4) proper and prudent prescribing of drugs (especially antibiotics) that are frequently associated with adverse reactions, (5) use of oral drugs when possible, and (6) documentation of ADR in the patient's medical record. (D)

*Summary Statement 60:* For some allergic drug reactions, withdrawal of the drug may be all that is required for treatment. (C)

*Summary Statement 61:* Anaphylactic drug reactions require prompt emergency treatment as discussed extensively in "The Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter." (B)

*Summary Statement 62:* Glucocorticosteroids may be required for immune complex reactions, drug-induced hematologic diseases, early stages of erythema multiforme major/Stevens-Johnson syndrome, and contact sensitivities. (C)

Drugs should be prescribed only for valid indications and combinations of drugs should be used sparingly. This is especially important in individuals who have had multiple reactions to various drugs. Ideally, ADRs should be prevented. Steps to prevent allergic drug reactions include (1) a careful history to determine host risk factors, (2) avoidance of cross-reactive drugs, (3) use of predictive tests when available, (4) proper and prudent prescribing of drugs (especially antibiotics) that are frequently associated with adverse reactions, (5) use of oral drugs when possible, and (6) documentation of ADR in the patient's medical record.

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 considered. Orally administered drugs are less likely to produce reactions than drugs given by the topical or parenteral route. MedicAlert tags and bracelets represent a useful way of alerting health care providers to a previous severe allergic reaction, although historical diagnoses of drug allergy may not be an indicator of current risk. Even so, the drug should not be given until the patient's current status is evaluated.

A few states now require that the names and concentrations of all medications appear on prescription labels. This is a useful advance that helps to ensure 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.

The management of drug allergy begins with the suspicion that any unexplained clinical manifestation may represent a

type B, unpredictable drug reaction. For some reactions, simple withdrawal of the drug may be all that is required for treatment. Acute anaphylactic reactions should be treated as described elsewhere.<sup>326</sup> Immune complex reactions usually resolve spontaneously once the antigen is cleared. However, therapy with antihistamines and possibly glucocorticosteroids and/or NSAIDs may be useful for control of urticaria, joint symptoms, or vasculitis. 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.

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 for which continued drug use may be justified are diabetic ketoacidosis, bacterial endocarditis, inflammatory bowel disease, neurosyphilis, AIDS, and pulmonary tuberculosis. Primary and secondary prevention of coronary artery disease and stroke may also justify the use of medications to which patients have experienced hypersensitivity reactions. When no equally effective alternative drug is available for therapy, the risk of continued administration of the offending drug may be less than the risk of not using the drug.

### B. Induction of Drug Tolerance

*Summary Statement 63:* What has often been referred to as drug desensitization is more appropriately described in this parameter as a temporary induction of drug tolerance. (D)

*Summary Statement 64:* Induction of drug tolerance modifies a patient's response to a drug to temporarily allow treatment with it safely. It is only indicated in situations where an alternate non-cross-reacting medication cannot be used. (B)

*Summary Statement 65:* Through various mechanisms, induction of drug tolerance procedures induce a temporary state of tolerance to the drug that is maintained only as long as the patient continues to take the specific drug. (B)

What has often been referred to as drug desensitization is more appropriately described in this parameter as a temporary induction of drug tolerance. Drug tolerance is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state of tolerance or that the mechanism involved was immunologic tolerance. Induction of drug tolerance procedures modify a patient's response to a drug to temporarily allow treatment with it safely. They are indicated only in situations where an alternate non-cross-reacting medication cannot be used. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms (Table 1). All procedures to induce drug tolerance involve administration of incremental doses of the drug. Through various mechanisms, these procedures induce a tem-

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porary state of tolerance to the drug that is maintained only as long as the patient continues to take the specific drug.

When there is a definite medical indication for the agent in question, either induction of tolerance or graded challenge procedures may be considered, depending on the history of the previous reaction and the likelihood that the patient is currently allergic to that agent. The goal of induction of tolerance is to modify an individual's immune response to a given drug to allow treatment with it safely. If there is a low likelihood of drug allergy, a graded challenge or test dose to the specific drug in question may provide a useful confirmation that administration of the drug will not result in an immediate reaction. The purpose of a graded challenge is to cautiously administer a drug to a patient who is unlikely to be allergic to it when there is no intention to alter the immune response. This differs from procedures that induce drug tolerance because graded challenges do not alter the patient's underlying sensitivity to the agent. Patients who tolerate a graded challenge are considered to not be allergic to the drug and are not at increased risk for future reactions compared with the general population. The use of prophylactic medications to prevent systemic reactions in these procedures is optional. These protocols require the supervision of a health care professional with previous experience performing these procedures.

The choice of whether to introduce a clinically indicated drug via graded challenge or via induction of drug tolerance mainly depends on the likelihood that the patient is allergic at the time of the procedure. Patients who, based on their history and/or diagnostic test results, are unlikely to be allergic to a drug may undergo graded challenge. For example, if penicillin skin testing is unavailable and a patient with a history of a mild pruritic rash during penicillin treatment 30 years ago requires penicillin therapy, it would be reasonable to administer penicillin via graded challenge. Patients who have a relatively higher likelihood of being allergic to a drug should undergo an induction of drug tolerance procedure. For example, if penicillin skin testing is unavailable and a patient with a recent history of penicillin-induced anaphylaxis requires penicillin, it should be administered via induction of drug tolerance. When the likelihood of allergy is unknown, patients should undergo induction of drug tolerance.

Graded challenge (or induction of drug tolerance) should almost never be performed if the reaction history is consistent with a severe non-IgE-mediated reaction, such as SJS, TEN, interstitial nephritis, hepatitis, or hemolytic anemia. Furthermore, these procedures are not indicated for all drug reactions, such as ACE inhibitor angioedema.

### **C. Immunologic IgE Induction of Drug Tolerance (Drug Desensitization)**

*Summary Statement 66:* Immunologic IgE induction of drug tolerance (drug desensitization) is the progressive administration of an allergenic substance to render effector cells less reactive. These procedures typically are done within

hours, and the typical starting dose is in the microgram range. (B)

Immunologic IgE induction of drug tolerance (also known as drug desensitization) is the progressive administration of an allergenic substance to render effector cells less reactive. These procedures typically are done within hours, and the typical starting dose is in the microgram range. The procedure can be performed via oral, intravenous, or subcutaneous routes. There are no comparative studies to compare the safety of different routes of induction of drug tolerance, such as oral vs intravenous. The resulting state is temporary, and its maintenance requires continued administration of the offending drug. Induction of drug tolerance procedures vary with individual drugs, and they are intended for agents that induce IgE-mediated reactions and, in some cases, for anaphylactoid (non-IgE-mediated anaphylaxis) reactions (such as for paclitaxel and other chemotherapeutic agents). For example, in penicillin induction of drug tolerance, the initial dose is typically approximately 1/10,000 of the full therapeutic dose.<sup>339-341</sup> Further dosage increases are typically twice the previous dose and are administered at 15- to 30-minute intervals until therapeutic levels are achieved. The duration of the procedure varies, depending on the drug and route of administration, but, in most cases, can be accomplished within 4 to 12 hours. Induction of drug tolerance should be performed in an appropriate setting, supervised by physicians familiar with the procedure, with continual monitoring of the patient and readiness to treat reactions, including anaphylaxis, should it occur. Induction of drug tolerance protocols are available for a variety of drugs, including virtually all classes of antibiotics, insulin, chemotherapeutic agents, and biological agents, such as humanized monoclonal antibodies.<sup>56,342-352</sup> In most cases, desensitization results in reversal of skin test reactivity from positive to negative.<sup>340,353-355</sup> Approximately a third of patients who undergo penicillin induction of drug tolerance experience allergic reactions, which are generally mild and occur predominantly after the procedure, during treatment with penicillin.<sup>339,340,353</sup> In the case of induction of drug tolerance with chemotherapeutics, 11% of patients experienced allergic reactions, none of which prevented completion of the procedure.<sup>356</sup> Example protocols for various Immunologic IgE induction of drug tolerance procedures are given in Tables 5, 6, 7, and 8.

### **D. Immunologic Non-IgE Induction of Drug Tolerance for Nonanaphylactic Reactions**

*Summary Statement 67:* For some delayed non-IgE-mediated cutaneous reactions, immunologic non-IgE induction of drug tolerance may be performed to allow treatment with the drug. However, it is generally contraindicated, with rare exceptions, for serious non-IgE-mediated reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis. One example of when the benefit of treatment may outweigh the risk of reaction is imatinib for treatment of malignant tumors. (C)

Table 5. Penicillin Oral Immunologic IgE Induction of Drug Tolerance (eg, Desensitization) Protocol.<sup>679</sup>

Step <sup>a</sup>	Penicillin, mg/mL	Amount, mL	Dose given, mg	Cumulative dose, mg
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5	1.2	6	12.35
9	5	2.4	12	24.35
10	5	5	25	49.35
11	50	1	50	100
12	50	2	100	200
13	50	4	200	400
14	50	8	400	800

Observe patient for 30 minutes, then give full therapeutic dose by the desired route.

<sup>a</sup> Interval between doses is 15 minutes.

Immunologic non-IgE induction of drug tolerance procedures are intended for patients who require a given drug to which they have previously experienced delayed non-IgE-mediated, typically cutaneous reactions. These are typically performed over hours to days with an initial dose in the milligram range.<sup>74,357,358</sup> Examples of reactions in which these procedures may be used are trimethoprim-sulfamethoxazole-induced typical delayed drug eruptions in human immunodeficiency virus-positive patients, as well as some delayed cutaneous reactions due to sulfasalazine. The mechanism of this drug tolerance induction procedure is unknown. For certain conditions (eg, SJS, TEN, exfoliative dermatitis), readministration is generally contraindicated, with rare exceptions, such as when benefit of treatment of a life-threat-

Table 6. Representative Paclitaxel Immunologic IgE Induction of Drug Tolerance (eg, Desensitization) Protocol.<sup>56</sup>

Step	Solution <sup>a</sup>	Rate, mL/h	Time, min	Dose given, mg	Cumulative dose, mg
1	A	2	15	0.006	0.006
2	A	5	15	0.015	0.021
3	A	10	15	0.03	0.051
4	A	20	15	0.06	0.111
5	B	5	15	0.15	0.261
6	B	10	15	0.3	0.561
7	B	20	15	0.6	1.161
8	B	40	15	1.2	2.361
9	C	10	15	3	5.361
10	C	20	15	6	11.361
11	C	40	15	12	23.361
12	C	75	221.3	276.639	300

<sup>a</sup> Solution A is 0.012 mg/mL (3 mg in 250 mL); solution B, 0.12 mg/mL (30 mg in 250 mL); and solution C, 1.2 mg/mL (300 mg in 250 mL).

Table 7. Example of Intravenous Cephalosporin IgE Induction of Drug Tolerance Protocol<sup>a</sup>

Preparation of Solutions					
	Volume of diluent (eg, 0.9% sodium chloride)	Total to be injected in each bottle	Final concentration, mg/mL		
Solution 1	250 ml	10 mg	0.04		
Solution 2	250 ml	100 mg	0.4		
Solution 3	250 ml	1000 mg	4		
Induction of Drug Tolerance Protocol					
Step	Solution	Rate, mL/h	Time, min	Administered dose, mg	Cumulative dose, mg
1	1	2	15	0.02	0.02
2	1	5	15	0.05	0.07
3	1	10	15	0.1	0.17
4	1	20	15	0.2	0.37
5	2	5	15	0.5	0.87
6	2	10	15	1	1.87
7	2	20	15	2	3.87
8	2	40	15	4	7.87
9	3	10	15	10	17.87
10	3	20	15	20	37.87
11	3	40	15	40	77.87
12	3	75	184.4	922.13	1000

<sup>a</sup> Full dose equals 1,000 mg. Total time was 349.4 minutes.

ening illness outweighs the risk of a potentially life-threatening reaction. Table 9 depicts a rapid (6-hour) procedure, whereas Table 10 depicts a slower 10-day outpatient procedure for immunologic non-IgE induction of drug tolerance to trimethoprim-sulfamethoxazole.

Table 8. Vancomycin Induction of Drug Tolerance Procedure<sup>344a</sup>

Time, min	Concentration of vancomycin, mg/mL	Infusion rate, mL/min	Vancomycin infusion rate, mg/min	Cumulative dose, mg
0	0.0001 <sup>b</sup>	1.0	0.00010	0
10	0.001	0.33	0.00033	0.0010
20	0.001 <sup>c</sup>	1.0	0.001	0.0043
30	0.01	0.33	0.0033	0.0143
40	0.01	1.0	0.01	0.047
50	0.1	0.33	0.033	0.147
60	0.1	1.0	0.1	0.48
70	1	0.33	0.33	1.48
80	1	1	1	4.78
90	10	0.22	2.2	14.8
100	10	0.44	4.4	37

<sup>a</sup> Rest of infusion maintained at 4.4 mg/min of vancomycin until final dosage reached. Antihistamine pretreatment and concurrent treatment used during protocol.

<sup>b</sup> Typical starting concentration in patients with severe vancomycin reactions.

<sup>c</sup> Typical starting concentration in patients with moderate vancomycin reactions.

Table 9. Six-Hour Trimethoprim-Sulfamethoxazole Induction of Drug Tolerance Procedure<sup>82a</sup>

Step	Drug dosage	Concentration of TMP-SMX	Volume of TMP-SMX solution, mL	Time, min
1	0.2/1 µg	8/40 µg/mL	0.025	0
2	0.6/3 µg	8/40 µg/mL	0.075	30
3	1.8/9 µg	8/40 µg/mL	0.225	60
4	6/30 µg	8/40 µg/mL	0.75	90
5	18/90 µg	8/40 µg/mL	2.25	120
6	60/300 µg	8/40 µg/mL	7.5	150
7	0.2/1 mg	80/400 µg/mL	2.5	180
8	0.6/3 mg	80/400 µg/mL	7.5	210
9	1.8/9 mg	0.8/4 mg/mL	2.25	240
10	6/30 mg	8/40 mg/mL	0.75	270
11	18/90 mg	8/40 mg/mL	2.25	300
12	60/300 mg	8/40 mg/mL	7.5	330

<sup>a</sup> Concentrations can be made by making 3 sequential 10-fold dilutions from the pediatric trimethoprim-sulfamethoxazole (TMP-SMX) solution available as 40/200/5 mL (8/40 mg/mL).

### E. Pharmacologic Induction of Drug Tolerance (eg, Aspirin Desensitization)

*Summary Statement 68:* Pharmacologic induction of drug tolerance to aspirin (eg, aspirin desensitization) is primarily intended for patients with aspirin-exacerbated respiratory disease (AERD), and unlike other types of desensitization, its purpose is to cautiously induce (rather than prevent) a reaction, after which patients become tolerant of aspirin and NSAIDs. (B)

Aspirin desensitization is a form of pharmacologic induction of drug tolerance. Similar to other induction of drug tolerance procedures, pharmacologic induction of drug tolerance procedures induce a temporary state of tolerance to aspirin that is maintained only as long as the patient continues to take aspirin. After aspirin desensitization, loss of tolerance generally returns in 2 to 4 days after discontinuation of continuous aspirin therapy.<sup>359</sup>

Pharmacologic induction of drug tolerance is typically performed in hours to days and generally starts with milligram amounts. It is commonly used for patients with AERD (see section VII.R). The protocol differs from both IgE and non-IgE induction of drug tolerance. It involves a metabolic shift, reduction in urinary leukotriene E4, internalization of cysteinyl leukotriene receptor 1 receptors, and, in some reports, release of mast cell tryptase. Precautions for aspirin desensitization should emphasize frequent monitoring of lung function and management of severe bronchospasm along with those used for other forms of induction of drug tolerance.

The most commonly cited and tested protocol (Table 11) involves incremental oral administration of aspirin during 2 to 4 days, starting at 15 to 30 mg and going to 650 mg.<sup>247,360,361</sup> Table 12 depicts a more practical protocol; however, there are no data on the safety and efficacy of this protocol. Continued daily administration of 325 to 650 mg of

aspirin is required for patients to remain in a tolerant state.<sup>359</sup> Leukotriene-modifying agents have been found to diminish the lower respiratory asthmatic response during aspirin desensitization and therefore should be considered as pretreatment for patients with AERD not already taking one of these agents.<sup>362,363</sup> Once patients are desensitized, universal cross-reactivity with all NSAIDs is achieved. One indication for aspirin desensitization is patients with AERD who require aspirin (eg, cardiovascular disease).<sup>364</sup> The other indication is poorly controlled AERD despite use of appropriate medications or patients who require long-term treatment with systemic corticosteroids to control their respiratory disease. Several long-term studies of patients maintained with long-term aspirin desensitization demonstrated improved clinical courses.<sup>247,360,361</sup> For upper respiratory tract disease, long-term aspirin desensitization was associated with significant improvements in nasal symptom scores, frequency of sinusitis, need for polypectomies or sinus operations, sense of smell, and dose of intranasal corticosteroids.<sup>247,360,361</sup> For lower respiratory tract disease, improved clinical outcomes included reductions in asthma symptom scores, hospitalizations, emergency department visits, and dose of inhaled corticosteroids.<sup>247,360,361,365</sup> Long-term aspirin desensitization also resulted in a reduction in the number of bursts of oral corticosteroids and allowed patients taking long-term corticosteroids to decrease their dose.<sup>247,360,361</sup>

In contrast to the aforementioned 2- to 4-day protocols for induction of drug tolerance to aspirin (aspirin desensitization) in patients with AERD, there are limited data on more rapid (2-5 hours) protocols in patients with histories predominantly of cutaneous reactions (urticaria or angioedema) to aspirin but also including a few patients with histories of respiratory reactions.<sup>364-367</sup> Although generally successful for most patients, patients with chronic urticaria or angioedema that is exacerbated by aspirin do not achieve tolerance via either rapid (2-5 hours) or standard (2-4 days) aspirin challenge or desensitization protocols and continue to experience flares of their cutaneous condition with exposure to aspirin or cross-

Table 10. Ten-Day Trimethoprim-Sulfamethoxazole Induction of Drug Tolerance Procedure<sup>680a</sup>

Day	Dosage, mg	Concentration/tablet	Amount
1	0.4/2	0.4/2 mg/mL	1 mL
2	0.8/4	0.4/2 mg/mL	2 mL
3	1.6/8	0.4/2 mg/mL	4 mL
4	3.2/16	0.4/2 mg/mL	8 mL
5	8/40	8/40 mg/mL	1 mL
6	16/80	8/40 mg/mL	2 mL
7	32/160	8/40 mg/mL	4 mL
8	64/320	8/40 mg/mL	8 mL
9	80/400	80/400-mg tablet	1 tablet
10	160/800	160/800-mg tablet	1 tablet

<sup>a</sup> The 0.4/2-mg/mL concentration can be made by making a 1:20 dilution of the pediatric Trimethoprim-sulfamethoxazole solution available as 40/200/5 mL (8/40 mg/mL).

Table 11. Aspirin Induction of Drug Tolerance Scripps Protocol<sup>681</sup>

Assessment and premedication (1-7 days before procedure)	FEV <sub>1</sub> >60% predicted (>1.5 L) Start or continue treatment with montelukast, 10 mg daily Start or continue treatment with inhaled corticosteroid and long-acting β-agonist Systemic steroid burst if low FEV <sub>1</sub> or bronchial instability
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Protocol	
Time	Aspirin Dose
Day 1: 0	30 mg
Day 1: 3 hours	60 mg
Day 1: 6 hours	100 mg
Day 2: 0	150 mg
Day 2: 3 hours	325 mg
Day 2: 6 hours	650 mg

Start intravenous catheter with heparin lock (keep in for 2-3 days).  
FEV<sub>1</sub> and clinical assessment every hour and with symptoms.  
Reactions typically occur with a provoking dose of 20-101mg.  
Treat with medications described below. Chance of reaction to repeated threshold dose is small, but if occurs, repeat dose until reactions cease and then proceed.

After patient completely stabilized, provoking dose can be repeated (assuming another 3 hours of observation time), otherwise start with provoking dose on day 2.

If nasal, gastrointestinal, or cutaneous reactions occur on day 1, pretreat with histamine<sub>1</sub> and histamine<sub>2</sub> receptor antagonists for remainder of procedure.

**Medications for treatment of aspirin-induced reactions**

Ocular	Topical antihistamines
Nasal	Antihistamine, topical decongestant
Laryngeal	Racemic epinephrine nebulization
Bronchial	β-Agonists
Gastrointestinal	Histamine <sub>2</sub> -receptor antagonists
Urticaria/angioedema	Antihistamine
Hypotension	Epinephrine

Abbreviation: FEV<sub>1</sub>, forced expiratory volume in 1 second.

reacting NSAIDs.<sup>366</sup> Although these protocols have been associated with success in allowing patients who otherwise would have been denied the benefits of aspirin to receive this drug safely, it is unclear whether these protocols truly induce drug tolerance (desensitization) or are simply a multistep graded-dose challenge. Most of the patients described in these reports required aspirin for acute coronary syndromes or before coronary stents and had a history of prior adverse reaction to aspirin. No confirmatory challenge studies could be performed to determine whether the previous reactions were causally or coincidentally associated with aspirin. For this reason, it is uncertain whether these patients were truly aspirin sensitive. An example of a rapid aspirin challenge desensitization protocol is provided in Table 13.

Table 12. Aspirin Induction of Drug Tolerance, Aspirin Desensitization Joint Task Force Recommendations<sup>682a</sup>

Assessment and premedication (within 1 week before procedure)	FEV <sub>1</sub> >70% predicted Consider starting or continuing leukotriene modifier therapy Start or continue treatment with high-dose inhaled corticosteroid and long-acting β-agonist if poorly controlled asthma Systemic steroid burst if low FEV <sub>1</sub> or bronchial instability If receiving maintenance systemic steroids, consider doubling daily dose (if on alternate day steroids change to daily dose)
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Protocol	
Time	Aspirin Dose
0	20.25 mg
90 min	40.5 mg
180 min	81 mg
270 min	162.5 mg
360 min	325 mg

Document informed consent and advise patient it may take several days to complete (most will take 2 days).  
Establish intravenous access.  
FEV<sub>1</sub> and clinical assessment every 90 minutes and with symptoms.  
Dosing interval may be extended to 3 hours based on individual patient characteristics.  
Reactions will likely occur with early doses, usually 81mg.  
Treat reactions as indicated below.

After patient completely stabilized (but not less than 3 hours after the last dose), the provoking dose can be repeated. A persistent >15% decrease in FEV<sub>1</sub>, with or without associated symptoms, lasting longer than 3 hours despite therapy, is an indication to discontinue the desensitization process for the day.

If nasal, gastrointestinal, or cutaneous reactions occur on day 1, pretreat with histamine<sub>1</sub> and histamine<sub>2</sub> receptor antagonists for remainder of procedure.

**Medications for treatment of aspirin-induced reactions**

Ocular	Oral antihistamines
Nasal	Oral antihistamine, topical decongestant
Laryngeal	Racemic epinephrine nebulization and/or intramuscular epinephrine
Bronchial	β-Agonists
Urticaria/angioedema	Oral or intravenous antihistamines
Hypotension	Parenteral epinephrine

Abbreviation: FEV<sub>1</sub>, forced expiratory volume in 1 second.  
<sup>a</sup> This recommended protocol is intended to be more practical, using doses based on commercially available 81 mg aspirin products and a shorter dosing interval. There are no data on safety and efficacy of this protocol.

Table 13. Rapid Aspirin Challenge/Desensitization Protocol for Patients With Coronary Artery Disease Requiring Aspirin<sup>366</sup>

Time <sup>a</sup>	Aspirin dose, mg
0	0.1
15	0.3
30	1
45	3
60	10
75	20
90	40
105	81
120	162
135	325

<sup>a</sup> Dosing interval shown is 15 minutes but may also dose every 20 minutes with premedication with oral antihistamine.

### F. Undefined Induction of Drug Tolerance

*Summary Statement 69:* Some induction of drug tolerance procedures have been described that appear to be successful through currently undefined mechanisms. (C)

Some induction of drug tolerance procedures have been reported for other drugs, but the mechanism of the adverse reaction to the drug and the mechanism of drug tolerance remains undefined. An example is the procedures (Tables 14 and 15) used to induce drug tolerance in patients with histories of cutaneous reactions to allopurinol. Although largely successful, these protocols have been associated with the subsequent development of significant adverse reactions.

### G. Graded Challenge

*Summary Statement 70:* The objective of a graded challenge is to cautiously introduce a drug in patients who are unlikely to be allergic to it. Unlike induction of drug tolerance, it does not modify patients' response to a drug. (D)

Graded challenge (also known as test dosing), unlike induction of drug tolerance, does not modify an individual's immune response to a given drug. The objective of a graded challenge is to introduce a medication cautiously so as not to

Table 14. Allopurinol (Standard Patient) Induction of Drug Tolerance Procedure<sup>358a</sup>

Daily dose	Concentration/tablet	Amount	Days
50 µg	1 mg/5 mL	0.25 mL	1-3
100 µg	1 mg/5 mL	0.5 mL	4-6
200 µg	1 mg/5 mL	1 mL	7-9
500 µg	1 mg/5 mL	2.5 mL	10-12
1 mg	1 mg/5 mL	5 mL	13-15
5 mg	10 mg/5 mL	2.5 mL	16-18
10 mg	10 mg/5 mL	5 mL	19-21
25 mg	10 mg/5 mL	12.5 mL	22-24
50 mg	100-mg tablet	½ tablet	25-27
100 mg	100-mg tablet	1 tablet	≥28

<sup>a</sup> Standard patient had a history of pruritic, erythematous exanthem after initiation of allopurinol with resolution of rash after drug therapy discontinuation.

Table 15. Allopurinol (High-Risk Patients) Induction of Drug Tolerance Procedure<sup>a</sup>

Daily dose	Concentration/tablet	Amount	Days
10 µg	1 mg/5 mL	0.05 mL	1-7
25 µg	1 mg/5 mL	0.12 mL	8-14
50 µg	1 mg/5 mL	0.25 mL	15-21
100 µg	1 mg/5 mL	0.5 mL	22-28
200 µg	1 mg/5 mL	1 mL	29-35
500 µg	1 mg/5 mL	2.5 mL	36-42
1 mg	1 mg/5 mL	5 mL	43-49
5 mg	10 mg/5 mL	2.5 mL	50-56
10 mg	10 mg/5 mL	5 mL	57-63
25 mg	10 mg/5 mL	12.5 mL	64-70
50 mg	100-mg tablet	½ tablet	71-77
100 mg	100-mg tablet	1 tablet	≥78

<sup>a</sup> High-risk patients were frail, elderly patients with multiple medical comorbid diseases, renal impairment, or more widespread eruptions, particularly if associated with fever.

induce a severe reaction.<sup>368</sup> Although it is not possible to be absolutely certain that a patient is not allergic to a drug because valid diagnostic tests are not available for most drugs, the procedure is intended for patients who, after a full evaluation, are unlikely to be allergic to the given drug. The starting dose for a graded challenge is higher than for induction of drug tolerance, and the number of steps in the procedure may be 2 or several. It is possible that a "graded challenge" consisting of more than 4 or 5 steps may induce modifications of immune effector cells and therefore induce drug tolerance in the patient. For that reason, future administrations of the drug should be given cautiously. The intervals between doses are dependent on the type of previous reaction, and the entire procedure may take hours or days to complete. Because parenteral administration of a drug is more likely to produce severe anaphylaxis than oral administration, more caution should be exercised for graded challenge procedures that use a parenteral route of administration.

One example of when a graded challenge may be appropriate is in penicillin skin test–positive patients who require treatment with cephalosporins because their reaction rate to cephalosporins is low (see section VII.A.4). Readministration of a drug via graded challenge is generally contraindicated if it caused a severe non-IgE-mediated reaction, such as SJS, TEN, or exfoliative dermatitis. Rare exceptions to this may exist, such as treatment of a life-threatening illness, in which case the benefit of treatment outweighs the risk of a potentially life-threatening reaction.

## VII. SPECIFIC DRUGS

Almost any drug is capable of inducing an allergic reaction and the likelihood that this will occur increases in direct proportion to the use 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

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section will discuss several of the most common clinical entities of drug hypersensitivity, some as representative examples of each of the 4 major Gell-Coombs categories of human hypersensitivity and others with heterogeneous and often unclassifiable immune characteristics.

## A. $\beta$ -Lactam Antibiotics

### 1. Penicillin

*Summary Statement 71:* Approximately 10% of patients report a history of penicillin allergy, but after complete evaluation, up to 90% of these individuals are able to tolerate penicillins. (B)

*Summary Statement 72:* Treatment of patients assumed to be penicillin allergic with alternate broad-spectrum antibiotics may compromise optimal medical care by leading to multiple drug-resistant organisms, higher costs, and increased toxic effects. (C)

*Summary Statement 73:* Evaluation of patients with penicillin allergy by skin testing leads to reduction in the use of broad-spectrum antibiotics and may decrease costs. (B)

*Summary Statement 74:* The rate of penicillin-induced anaphylaxis after parenteral administration is about 1 to 2 per 10,000 treated patients. (C)

*Summary Statement 75:* Penicillin is immunologically inert and haptens proteins after undergoing spontaneous conversion under physiologic conditions to reactive intermediates. These transformation products are known as penicillin major and minor antigenic determinants. (C)

*Summary Statement 76:* Penicillin skin testing is the most reliable method for evaluating IgE-mediated penicillin allergy. (B) Ideally, penicillin skin testing should be performed with both major and minor determinants. The negative predictive value of penicillin skin testing for immediate reactions approaches 100%, whereas the positive predictive value is between 40% and 100%. (B)

*Summary Statement 77:* Skin testing with the major determinant and penicillin G only (without penicilloate and penicilloate) may miss up to 20% of allergic patients, but data on this are conflicting. (C)

*Summary Statement 78:* Penicillin G left in solution ("aged" penicillin) does not spontaneously degrade to form antigenic determinants and has no role in penicillin skin testing. (B)

*Summary Statement 79:* Penicillin skin testing without the major determinant is not recommended because this would fail to identify many patients with penicillin specific IgE antibodies. (B)

*Summary Statement 80:* When performed by skilled personnel using proper technique, serious reactions due to penicillin skin testing are extremely rare. (C)

*Summary Statement 81:* Penicillin skin testing may be performed electively—when patients are well and not in immediate need of antibiotic therapy. Alternatively, penicillin skin testing may be performed when treatment with a penicillin compound is contemplated. (D)

*Summary Statement 82:* Patients who have had negative skin test results to penicillin major and minor determinants may receive penicillin with minimal risk of an IgE-mediated reaction. Depending on the reaction history, the first dose may need to be given via graded challenge. (D)

*Summary Statement 83:* Penicillin skin test–positive patients should avoid penicillin, but if they develop an absolute need for penicillin, rapid induction of drug tolerance may be performed. (B)

*Summary Statement 84:* Resensitization after treatment with oral penicillin is rare, and therefore penicillin skin testing does not routinely need to be repeated in patients with a history of penicillin allergy who have tolerated 1 or more courses of oral penicillin. (B)

*Summary Statement 85:* Resensitization after treatment with parenteral penicillin appears to be higher than for oral treatment, and therefore repeat penicillin skin testing may be considered in patients with a history of penicillin allergy who have tolerated a course of parenteral penicillin. (C)

*Summary Statement 86:* The negative predictive value of penicillin skin testing without penicilloylpolylysine is poor because many allergic patients show skin test reactivity only to the major determinant. (B)

*Summary Statement 87:* When penicillin skin testing is unavailable, evaluation of penicillin allergy is based on the reaction history and likelihood of needing treatment with penicillins. (C)

*Summary Statement 88:* Patients with a vague and/or distant history of penicillin allergy may be candidates to receive penicillins via graded challenge. Patients with recent or convincing reaction histories should only receive penicillins via rapid induction of drug tolerance. (C)

*Summary Statement 89:* The usefulness of in vitro tests for penicillin specific IgE is limited by their uncertain predictive value. They are not suitable substitutes for penicillin skin testing. (C)

Approximately 10% of patients report a history of reacting to a penicillin class antibiotic. When evaluated for penicillin allergy, up to 90% of these individuals are able to tolerate penicillins and therefore are designated as being penicillin allergic unnecessarily.<sup>17,18,369</sup> There are several explanations to account for this discrepancy. Penicillin specific IgE antibodies are known to rapidly wane over time.<sup>370</sup> It is likely that some reactions, particularly cutaneous eruptions, were the result of an underlying viral or bacterial infection or an interaction between the infectious agent and the antibiotic.<sup>371,372</sup> Some patients may mislabel the antibiotic they were treated with as penicillin or may attribute predictable reactions (ie, diarrhea or vaginitis) as allergic.

Although most patients with a history of penicillin allergy could tolerate penicillin, clearly there is potential for serious and life-threatening immediate-type reactions to penicillin if it is readministered.<sup>302</sup> For this reason, physicians are faced with antibiotic choices that may be less effective, more toxic, or more expensive and may compromise optimal medical care.<sup>19,373-377</sup> In addition, in the era of multiple anti-

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microbial drug resistance, the use of broad-spectrum antibiotics in patients designated as being penicillin allergic augments this problem.<sup>19,374,378,379</sup> A number of medical centers have used penicillin skin testing (many using only penicilloylpolylysine and penicillin G as skin test reagents) in patients with a history of penicillin allergy to reduce the use of broad-spectrum antibiotics and improve use of antibiotic selections.<sup>377,380-384</sup>

There are few prospective data on the rate of penicillin sensitization. Among military recruits without a history of penicillin allergy, 51 of 614 patients (8.2%) converted from a negative to positive penicillin skin test result (using penicilloylpolylysine as the only reagent) after a single injection of benzathine penicillin G.<sup>385</sup> Most penicillin class antibiotic reactions involve cutaneous eruptions, and in a large-scale review of adverse skin reactions of the Boston Collaborative Drug Surveillance Program, the frequency of skin reactions was 5.1% with amoxicillin, 4.5% with ampicillin, and 1.6% with penicillin.<sup>305</sup> Most of these reactions were macular, morbilliform, or urticarial, and it is unclear how many were IgE dependent. Life-threatening anaphylactic reactions to penicillin are of the most concern, and they appear to be rare. In 1968, in a review of published and unpublished reports, the rate of penicillin-induced anaphylaxis was 0.015% to 0.04% of treated patients.<sup>302</sup> In a study of children and young adults receiving monthly injections of benzathine penicillin G for an average of 3.4 years, the incidence of anaphylaxis was 1.23 per 10,000 injections, but none occurred in the 600 patients younger than 12 years.<sup>386</sup> Among healthy military recruits, 2 of 9,203 experienced anaphylaxis after prophylactic treatment with a single dose of benzathine penicillin (ie, 2.17 per 10,000).<sup>387</sup>

Penicillin is chemically inert in its native state and can only haptenate proteins after undergoing conversion to reactive intermediates. This process occurs spontaneously under physiologic conditions, whereas most other antibiotics must be metabolized enzymatically to produce intermediates capable of binding to host proteins. The penicillin molecule has a core bicyclic structure composed of a 4-member  $\beta$ -lactam ring and a 5-member thiazolidine ring. Under physiologic conditions, the  $\beta$ -lactam ring opens spontaneously, allowing the carbonyl group to form an amide linkage with amino groups of lysine residues on nearby proteins.<sup>388,389</sup> This penicilloyl group comprises approximately 95% of the tissue-bound penicillin and therefore is called the major antigenic determinant. The remaining portion of penicillin either remains in the native state or degrades further to a variety of minor antigenic determinants capable of haptening proteins. The most important of these are penicilloate and penilloate, and they, along with penicillin itself, cover all clinically relevant allergenic determinants not covered by penicilloyl and are not cross-reactive with one another.<sup>390</sup>

Immediate-type penicillin allergy cannot be accurately diagnosed by history alone. This observation is partially explained by the fact that patients with convincing reaction histories lose their sensitivity over time. In addition, patients

with vague reaction histories may be allergic and demonstrate positive skin test results.<sup>375,391,392</sup> Overall, approximately one-third of patients with positive penicillin skin test results report vague reaction histories.<sup>393</sup> Penicillin skin testing is the most reliable method for evaluating IgE-mediated penicillin allergy. In vitro tests (radioallergosorbent test or enzyme-linked immunoassay) are less sensitive and specific compared with skin testing.<sup>394</sup> Penicillin skin testing detects the presence or absence of penicillin specific IgE antibodies, and it is not useful or indicated for clearly non-IgE-mediated reactions.

Ideally, both major and minor determinant reagents are used for skin testing. The major determinant has been commercially available as penicilloylpolylysine (PRE-PEN) in a premixed  $6 \times 10^{-5}$ M solution. Of the minor determinants, penicillin G is commercially available and should be used for skin testing at a concentration of 10,000 U/mL. The other minor determinants (penicilloate and penilloate) are used for skin testing at 0.01M but have never been commercially available in the United States. Penicillin G left in solution ("aged" penicillin) does not spontaneously degrade to form other minor determinants and therefore cannot be used as a substitute for the other minor determinants.<sup>395</sup> The negative predictive value of penicillin skin testing (using penicilloylpolylysine, penicillin G and penicilloate, and/or penilloate) for serious immediate-type reactions approaches 100%,<sup>17,18,396</sup> and the positive predictive value (based on limited challenges of skin test-positive patients) is between 40% and 100%.<sup>17,396,397</sup>

Because penicilloate and penilloate have never been commercially available in the United States, most allergists perform penicillin skin tests with only penicilloylpolylysine and penicillin G. However, some studies report that approximately 10% to 20% of penicillin-allergic patients show skin test reactivity only to penicilloate or penilloate.<sup>17,18,391,398</sup> The clinical significance of these findings is uncertain. Penicillin challenges of individuals skin test negative to penicilloylpolylysine and penicillin G<sup>397,399</sup> have similar reaction rates compared with individuals skin test negative to the full set of major and minor penicillin determinants.<sup>17,18,396</sup> Therefore, based on the available literature, skin testing with penicilloylpolylysine and penicillin G appears to have adequate negative predictive value in the evaluation of penicillin allergy.

Penicillin skin testing should only be performed by personnel skilled in the application and interpretation of this type of skin testing, with preparedness to treat potential anaphylaxis.<sup>400</sup> Appropriate positive (histamine) and negative (saline) controls should be placed. First, full-strength reagents are applied by the prick/puncture technique, and if these results are negative, intradermal testing should be performed. There is no uniform agreement on what constitutes a positive skin test response, but most experts agree that it is defined by the size of the wheal, which should be 3 mm or greater than that of the negative control for either prick/puncture or intradermal tests. Penicillin skin testing, using the reagents described above and proper technique, are safe with only a rare risk of a systemic reactions occurring.<sup>18,401</sup>

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Penicillin skin testing appears to sensitize a small percentage of patients. Of 239 patients with initially negative penicillin skin test results, 6 patients (2.5%) converted to a positive skin test 1 month later (without any treatment with penicillin).<sup>402</sup> The clinical significance of this skin test conversion is unknown because none of the patients were subsequently challenged with penicillin. In a previous study, among 614 patients without a history of penicillin allergy, 51 (8.2%) converted from a negative to positive skin test result (using penicilloylpolylysine as the only reagent) after a single injection of penicillin G.<sup>385</sup> Each of these 51 patients was then given a second injection of penicillin G and none experienced a reaction.

Penicillin skin testing is indicated in patients who have a reaction history consistent with a possible IgE-mediated mechanism. Penicillin skin testing may be performed electively (when patients are well and not in immediate need of antibiotic therapy) or only when treatment with a penicillin compound is contemplated. Arguments in favor of elective skin testing include the fact that penicillin skin testing in the acute setting when a patient is ill is more difficult to accomplish in a timely fashion. Consequently, such patients are treated with alternate antibiotics,<sup>19,374,376,393</sup> many of which, such as vancomycin and fluoroquinolones, have a broader spectrum of antimicrobial activity or may be more toxic or expensive. Overuse of broad-spectrum antibiotics is known to contribute to the development and spread of multiple antibiotic resistance.<sup>378,379,403</sup> Arguments in favor of testing at time of need include the potential of skin testing or the subsequent course of penicillin (in skin test–negative individuals) to induce resensitization and hence the need to repeat penicillin skin testing before each future course.

There is lack of agreement regarding the need, immediately after a negative penicillin skin test result, to perform an elective challenge with penicillin. Surveys of patient with negative penicillin skin test results (without subsequently being challenged with penicillin) found that a large proportion was not treated with  $\beta$ -lactam antibiotics because of fear on either the part of the patient or the treating physician.<sup>404</sup> In an enclosed health maintenance organization setting, review of medical records found that subsequent prescriptions for penicillins in penicillin skin test–negative patients were comparable in those individuals who were and were not challenged with oral penicillin after their skin test (47% vs 48% during the year after the skin test).<sup>380</sup> If penicillin skin testing is performed with only penicilloylpolylysine and penicillin G, initial administration of penicillin, depending on the pretest probability of the patient being allergic, may need to be done via graded challenge (ie, 1/100 of the dose, followed by the full dose, assuming no reaction occurs during a brief observation period).

Several studies have addressed the issue of resensitization (ie, redevelopment of penicillin allergy) in patients with a history of penicillin allergy who later demonstrate negative penicillin skin test results. Resensitization after oral treatment with penicillin is rare in both pediatric and adult patients,

including after repeated courses.<sup>369,380,405,406</sup> Hence, routine repeat penicillin skin testing is not indicated in patients with a history of penicillin allergy who have tolerated 1 or more oral courses of oral penicillin. Consideration may be given to retesting individuals with recent or particularly severe previous reactions. Resensitization after high-dose parenteral treatment with penicillin appears to be more likely; therefore, repeat penicillin skin testing in this situation may be warranted.<sup>407,408</sup>

The approach to evaluation of penicillin allergy in the absence of penicilloylpolylysine is different compared with when the major determinant is available. Omission of penicilloylpolylysine from the penicillin skin testing panel results in a failure to identify many penicillin-allergic individuals. Depending on the population studied, as many as 75% of penicillin skin test–positive patients showed positive responses to only penicilloylpolylysine.<sup>18,398,409</sup> As a result, the negative predictive value of penicillin skin testing without penicilloylpolylysine is poor, and, in that situation, elective penicillin skin testing is not recommended. Also, in remote areas, clinicians may not have access to an allergist/immunologist to perform penicillin skin testing even if appropriate reagents are available.

Without penicillin skin testing, the approach to patients with a history of penicillin allergy is based on the reaction history and likelihood of needing treatment with penicillins. One such group of patients is those who report reactions to many different classes of antibiotics and thus are “running out” of antibiotic choices. Patients with convincing reaction histories are more likely to be allergic than patients with vague reaction histories.<sup>18,397,410,411</sup> However, as discussed earlier, vague reaction histories cannot be completely discounted because those patients may also be penicillin allergic.<sup>375,391,392</sup> The time elapsed since the reaction is useful because penicillin specific IgE antibodies wane over time, and therefore patients with recent reactions are more likely to be allergic than patients with distant reactions. Approximately 50% of patients with IgE-mediated penicillin allergy lose their sensitivity 5 years after reacting, and this percentage increases to approximately 80% in 10 years.<sup>370,412</sup> Recently, a study of 169 patients with a non–life-threatening history of penicillin allergy and who had avoided penicillin for more than 3 years were evaluated by penicillin skin tests with major and minor determinants and graded challenge, regardless of whether the penicillin skin test result was positive or negative.<sup>413</sup> A low rate of positive penicillin challenges occurred in both groups, which was not statistically different (6.6% in the penicillin skin test–positive group and 3.7% in the penicillin skin test–negative group). This study suggests that penicillin specific IgE in some patients may indicate sensitization rather than true clinical allergy. Patients with distant (longer than 10 years) or questionable reaction histories (eg, vague childhood rash), due to their relatively low likelihood of being penicillin allergic, may be candidates to receive penicillin via graded challenge, as opposed to induction of drug tolerance procedure. In contrast, if there is a convincing history of an

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IgE-mediated reaction to penicillin (eg. anaphylaxis), particularly if the reaction was recent, penicillin should be administered via induction of drug tolerance procedure. Clinical judgment is required to carefully weigh the risks and benefits of either procedure and informed consent (verbal or written) of the patient in determining which type of procedure is in the patient's best interest.

In vitro tests for IgE directed against penicilloylpolylysine, penicillin G, penicillin V, amoxicillin, and ampicillin are commercially available, but they are not suitable alternatives to skin testing because these assays have unknown predictive value, which limits their usefulness. When performed in academic settings, the sensitivity of in vitro tests for penicillin specific IgE was as low as 45% compared with skin testing.<sup>414,415</sup> A positive penicillin in vitro test result in the context of an appropriate reaction history suggests presence of an IgE-mediated allergy; however, a negative in vitro test result does not rule out an IgE-mediated allergy.

## 2. Ampicillin and Amoxicillin

*Summary Statement 90:* Some patients with immediate-type reactions to amoxicillin and ampicillin have IgE antibodies directed at the R-group side chain (rather than the core penicillin determinants) and are able to tolerate other penicillin class compounds. (C)

*Summary Statement 91:* Amoxicillin and ampicillin are associated with the development of a delayed maculopapular rash in approximately 5% to 10% of patients. (C) These reactions are not related to IgE-mediated allergy, and they are postulated in many cases to require the presence of a concurrent viral infection or another underlying illness. (D)

Some patients with immediate-type reactions to amoxicillin or ampicillin are able to tolerate other penicillin class compounds.<sup>416-418</sup> These individuals appear to have reactions directed at the R-group side chain, which distinguishes the chemical structure of different penicillin class compounds. These patients may have skin test results that are positive to a nonirritating concentration of either amoxicillin or ampicillin but test negative to penicillin major and minor determinants.<sup>416-418</sup> Therefore, skin testing of patients who have reacted to semisynthetic penicillins with the implicated antibiotic and penicillin major and minor determinants may add additional useful information. The negative predictive value of skin testing with native semisynthetic penicillins is unknown, and there is no consensus regarding the appropriate concentration that should be used.

Administration of ampicillin and amoxicillin is associated with the development of a delayed maculopapular rash in 5% to 10% of patients.<sup>419</sup> These patients are not at risk of a life-threatening immediate reaction to penicillin. Most patients will tolerate future administration of penicillin other than ampicillin and amoxicillin. If ampicillin or amoxicillin is administered again, the patient may develop a similar eruption or no reaction at all. It is postulated that many amoxicillin/ampicillin-associated delayed maculopapular rashes require the presence of a concurrent viral illness. In the case of

patients with Epstein-Barr virus infections, almost 100% will develop a nonpruritic rash.<sup>371,372</sup> The incidence of nonpruritic, 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>420,421</sup> Because patients' reaction histories are known to be a poor predictor of skin test results,<sup>375,392</sup> penicillin skin testing should be considered even in patients with a history suggestive of amoxicillin/ampicillin-associated maculopapular rashes before a future course of penicillin is given. If the penicillin skin test result is negative, the patient should be approached as outlined in the prior discussion about penicillin. If the penicillin skin test result is positive, the patient should be given an alternative antibiotic or undergo induction of drug tolerance to penicillin.

## 3. Cephalosporins (Figure 2)

*Summary Statement 92:* The overall reaction rate to cephalosporins is approximately 10-fold lower than it is for penicillin. (C)

*Summary Statement 93:* Most hypersensitivity reactions to cephalosporins are probably directed at the R-group side chains rather than the core  $\beta$ -lactam portion of the molecule. (D)

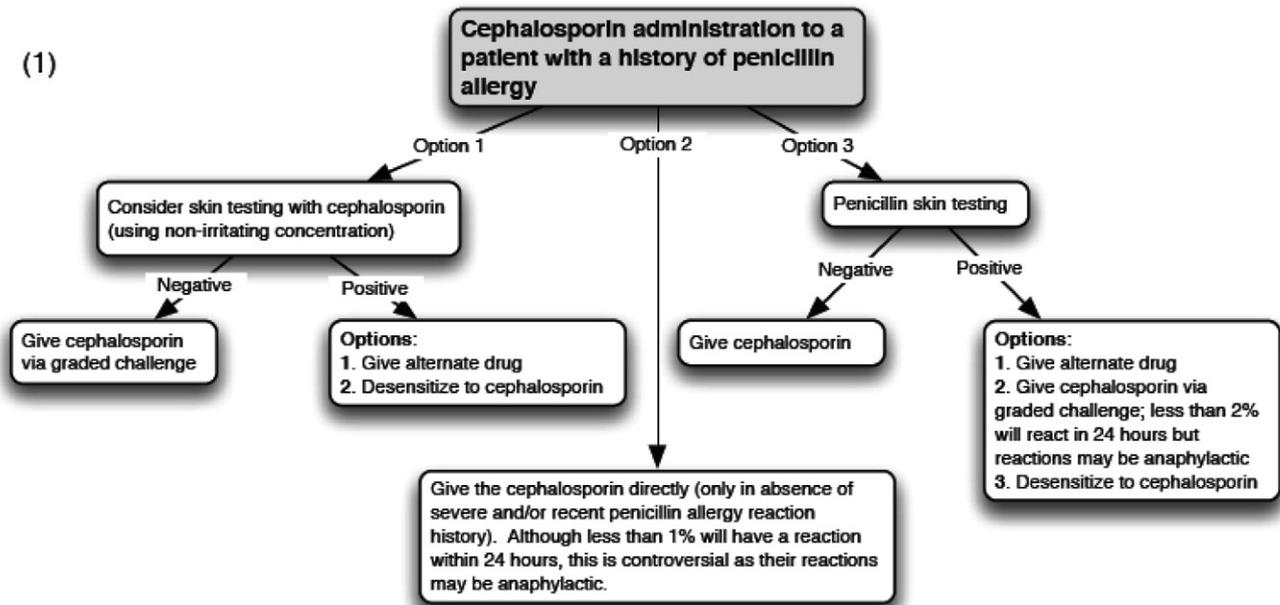
*Summary Statement 94:* Skin testing with native cephalosporins is not standardized, but a positive skin test result using a nonirritating concentration suggests the presence of drug specific IgE antibodies. (D) A negative skin test result does not rule out an allergy because the negative predictive value is unknown. (D)

*Summary Statement 95:* Patients with a history of an immediate-type reaction to 1 cephalosporin should avoid cephalosporins with similar R-group side chains. (D) Treatment with cephalosporins with dissimilar side chains may be considered, but the first dose should be given via graded challenge or induction of drug tolerance, depending on the severity of the previous reaction. (D)

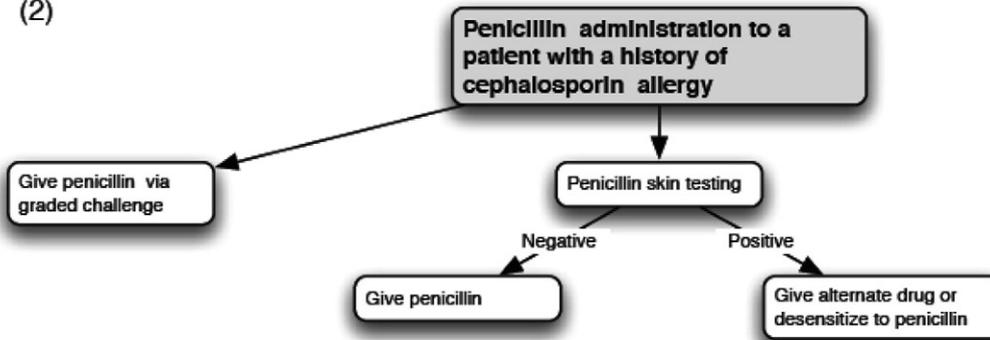
*Summary Statement 96:* Cephalosporins and penicillins share a common  $\beta$ -lactam ring structure and moderate cross-reactivity has been documented in vitro. (B)

Overall, the rate of allergic reactions to cephalosporins is approximately 10-fold lower than it is to penicillin.<sup>422</sup> Anecdotal evidence suggests that allergic reactions to cephalosporins are directed at the R-group side chains rather than the core  $\beta$ -lactam portion of the molecule.<sup>423-427</sup> However, there are no clinical challenge studies to prove that patients allergic to one cephalosporin are able to tolerate other cephalosporins with dissimilar side chains. If a patient with a history of allergy to one cephalosporin requires treatment with another cephalosporin, the following approach may be considered: (1) after ensuring that 2 cephalosporins do not share R-group side chains, perform a graded challenge with the new cephalosporin; (2) perform cephalosporin skin testing (with the agent to be used), although such skin testing is not standardized and the negative predictive value is unknown; or (3) perform cephalosporin induction of drug tolerance, particu-

(1)



(2)



(3)

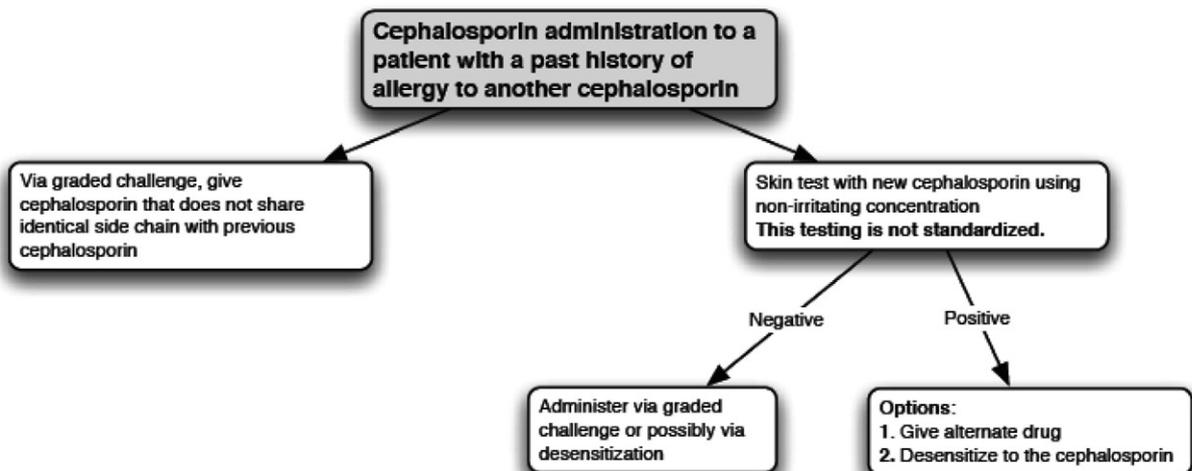


Figure 2. Cephalosporin algorithms.

larly if there is a history of severe anaphylaxis. Ten-fold dilutions of native cephalosporins have been reported to be nonirritating,<sup>428</sup> but each cephalosporin may require concurrent evaluation for its irritation potential in nonallergic patients. Skin testing should be performed as described in the penicillin section with a prick/puncture test 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 a further 10-fold dilution or lower. A positive cephalosporin skin test result (using a nonirritating concentration) implies the presence of drug specific IgE antibodies, and the patient should receive an alternate drug or undergo induction of drug tolerance. A negative cephalosporin skin test (using a nonirritating concentration) does not rule out the presence of drug specific IgE antibodies. IgE antibodies to cephalosporin degraded products not used in the testing may be present but not detectable. Therefore, because the negative predictive value of cephalosporin skin testing is unknown, a cautious graded challenge should be performed (eg, 1/100 of the therapeutic dose, increasing 10-fold every 30 to 60 minutes up to the full therapeutic dose). The number of steps in the graded challenge and the pace of the challenge are determined by the reaction history. Graded challenges require may be performed in an outpatient setting, without intravenous access, but with preparedness to treat severe allergic reactions, such as anaphylaxis. If the previous history is consistent with a severe IgE-mediated reaction, induction of drug tolerance with the cephalosporin may be undertaken instead.

#### **4. Cephalosporin Administration to Patients With a History of Penicillin Allergy (Figure 2)**

*Summary Statement 97:* Since 1980, studies show that approximately 2% of penicillin skin test–positive patients react to treatment with cephalosporins, but some of these reactions may be anaphylactic reactions. (C)

*Summary Statement 98:* Without preceding penicillin skin testing, cephalosporin treatment of patients with a history of penicillin allergy, selecting out those with severe reaction histories, show a reaction rate of 0.1% based on recent studies. (C)

*Summary Statement 99:* Penicillin skin testing, when available, should be considered before administration of cephalosporins in patients with a history of penicillin allergy. (E)

*Summary Statement 100:* Patients who have a history of a possible IgE-mediated reaction to penicillin, regardless of the severity of the reaction, may receive cephalosporins with minimal concern about an immediate reaction if skin test results for penicillin major and minor determinants are negative. (B)

*Summary Statement 101:* Treatment options for penicillin skin test–positive patients include (1) administration of an alternate (non- $\beta$ -lactam) antibiotic, (2) administration of cephalosporin via graded challenge, or (3) administration of cephalosporin via rapid induction of drug tolerance. (E)

*Summary Statement 102:* Skin testing to the cephalosporin followed by graded challenge appears to be a safe method for administration of some cephalosporins in penicillin allergic patients. (B)

*Summary Statement 103:* If penicillin and cephalosporin skin testing is unavailable, depending on the reaction history, cephalosporins may need to be given via graded challenge or rapid induction of drug tolerance. (E)

Cephalosporins and penicillins have a common  $\beta$ -lactam ring structure and moderate cross-reactivity has been documented in vitro.<sup>429-431</sup> Most of the in vitro cross-reactions between penicillins and cephalosporins have involved first- and second-generation cephalosporins.<sup>429-431</sup> Although clinically significant cross-reactivity between penicillin and the cephalosporins is infrequent, anaphylactic reactions after administration of cephalosporin have occurred in patients with a history of penicillin allergy.<sup>23,432-436</sup> Before 1980, penicillin allergy history–positive and skin test–positive patients who were given cephalosporins had a reaction rate of approximately 10% to 20%.<sup>430,437</sup> Since 1980, reaction rates in penicillin history–positive and skin test–positive patients treated with cephalosporins have decreased to 2%.<sup>22,438-440</sup> Before 1980, all penicillin allergic patients who reacted to a cephalosporin had been treated with cephalothin or cephaloridine. Benzyl penicillin and these cephalosporins 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.<sup>441</sup> Since 1980, contamination of this type has not been documented.

If patients with a history of allergy to penicillin are not skin tested but given cephalosporins directly, the chance of a reaction is probably less than 1%. This figure is based on the fact that only approximately 10% of penicillin history–positive patients have positive skin test results,<sup>17,18</sup> and of those, only 2% will react to a cephalosporin.<sup>22,438-440</sup> This finding may be interpreted to mean that skin testing is unnecessary because a 2% reaction rate may occur even without a prior history of allergy. However, some of these reactions were fatal anaphylaxis.<sup>23,435</sup> Patients with a history of penicillin allergy who have negative skin test results to penicillin using major and minor determinants may receive cephalosporins safely.<sup>24</sup>

Recent retrospective studies of administration of mostly parenteral cephalosporins to patients with a history of penicillin allergy, without prior penicillin skin testing, have shown only 2 possible cephalosporin allergic reactions among 906 patients, neither of which appeared to be IgE mediated.<sup>442,443</sup> However, there was probably a selection bias in deciding which patients were treated with cephalosporins instead of non- $\beta$ -lactam antibiotics. Physicians in these “real-world” studies were probably less likely to treat with cephalosporins if patients had more severe or recent reaction histories, and, in some cases, pharmacists intervened to prevent patients with severe reaction histories from receiving cephalosporins.<sup>443</sup>

Table 16. Groups of  $\beta$ -Lactam Antibiotics That Share Identical R<sub>1</sub>-Group Side Chains<sup>a</sup>

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephadrine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

<sup>a</sup> Each column represents a group with identical R<sub>1</sub> side chains.

It is also possible that some patients with a history of penicillin allergy react to cephalosporins because of their underlying propensity to develop reactions to unrelated drugs rather than allergic cross-reactivity between the  $\beta$ -lactams. In patients with documented allergic-like reactions to penicillins, the relative risk for allergic-like reactions was elevated for both cephalosporins and sulfonamides.<sup>307</sup>

Nevertheless, because of these disparate observations, there is not a common consensus regarding the management of a patient with a 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; (2) perform penicillin skin testing; (3) perform cephalosporin skin test and if the result is negative perform a graded challenge; or (4) treat with the cephalosporin. The fourth option should be considered only in the absence of a severe and/or recent penicillin allergy reaction history. If the penicillin skin test result is negative, the patient can receive the cephalosporin. If the skin test result is positive, there may be a slightly increased risk of a reaction if the cephalosporin is given and cephalosporin should be administered via graded challenge or rapid induction of drug tolerance. Skin testing to cephalosporins may also be considered for patients with a history of penicillin allergy. One study evaluated 128 patients with convincing histories of penicillin allergy and confirmed by positive penicillin skin test results.<sup>22</sup> Of these 128 subjects, 114 had negative intracutaneous skin test results to cephalosporins at 2 mg/mL, 90 underwent challenges to cefuroxime and ceftriaxone, and all the results were negative. Therefore, particularly in patients with convincing histories for penicillin allergy who require cephalosporins, skin testing to the cephalosporin followed by graded challenge appears to be a safe method for administration of cephalosporins.

Allergic cross-reactivity between amoxicillin and cephalosporins that share identical R-group side chains is higher than for penicillin skin test–positive patients. Twelve percent to 38% of patients proven to be selectively allergic to amoxicillin (ie, able to tolerate penicillin) reacted to ce-

fadroxil.<sup>444,445</sup> Therefore, amoxicillin allergic patients should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine) or receive them via rapid induction of drug tolerance (Table 16). Similarly, ampicillin allergic patients should avoid cephalexin, cefaclor, cephradine, cephaloglycin, and loracarbef or receive them via rapid induction of drug tolerance (Table 17).

## 5. Penicillin Administration to Patients With a History of Cephalosporin Allergy (Figure 2)

**Summary Statement 104:** Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine) or receive them via rapid induction of drug tolerance. (C) Similarly, patients allergic to ampicillin should avoid cephalosporins/carbacephems with identical R-group side chains (cephalexin, cefaclor, cephradine, cephaloglycin, loracarbef) or receive them via rapid induction of drug tolerance. (C)

**Summary Statement 105:** Patients with a history of an immediate-type reaction to a cephalosporin should undergo penicillin skin testing, if available, before treatment with penicillin. (E) If test results are negative, they may safely receive penicillins. (B) If test results are positive, an alternate drug should be used or they should undergo rapid penicillin induction of drug tolerance. (B) If penicillin skin testing is unavailable, penicillin may be administered via cautious graded challenge. (C)

Patients with a history of an immediate-type allergic reaction to a cephalosporin who require penicillin should undergo penicillin skin testing. If results are negative, they can receive penicillin; if results are positive, they should receive an alternate drug or undergo penicillin induction of drug tolerance. If penicillin skin testing is unavailable, because the likelihood of reaction is low, cautious graded challenge with penicillin may be considered in patients with a history of immediate-type allergy to cephalosporins. If a patient has a history of a non-IgE-mediated reaction to cephalosporin (other than serious reactions such as SJS or TEN) and re-

Table 17. Groups of  $\beta$ -Lactam Antibiotics That Share Identical R<sub>2</sub>-Group Side Chains<sup>a</sup>

Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephadrine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

<sup>a</sup> Each column represents a group with identical R<sub>2</sub> side chains.

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quires penicillin, a graded challenge with penicillin may be performed and skin testing is not indicated.

## 6. Monobactams (Aztreonam)

*Summary Statement 106:* Aztreonam is less immunogenic than penicillin and cephalosporins, and clinical allergic reactions to aztreonam are less common than other  $\beta$ -lactam antibiotics. (C)

*Summary Statement 107:* Aztreonam does not cross-react with other  $\beta$ -lactams except for ceftazidime, with which it shares an identical R-group side chain. (B)

Aztreonam is less immunogenic than both penicillin and cephalosporins,<sup>446</sup> and clinical experience confirms that allergic reactions to aztreonam appear to be uncommon. Evaluation of IgE-mediated allergy to aztreonam is analogous to cephalosporins in that relevant allergenic degradation products are unknown, and thus there are no standardized skin test reagents available. Skin testing with a nonirritating concentration of native aztreonam has the same limitation and questionable predictive value as with cephalosporins.

In vitro tests, skin tests, and patient challenge studies have consistently shown no cross-reactivity between penicillin and aztreonam.<sup>447-452</sup> Likewise, no cross-reactivity has been demonstrated between cephalosporins and aztreonam, except for ceftazidime, which shares an identical R-group side chain with aztreonam.<sup>315,446,449</sup> Therefore, penicillin and cephalosporin allergic patients may safely receive aztreonam, with the exception of patients who are allergic to ceftazidime. Conversely, aztreonam allergic patients may be treated with all  $\beta$ -lactams except for ceftazidime.

## 7. Carbapenems

*Summary Statement 108:* Limited data indicate lack of significant allergic cross-reactivity between penicillin and carbapenems. (B) Penicillin skin test–negative patients may safely receive carbapenems. (C) Penicillin skin test–positive patients and patients with a history of penicillin allergy who do not undergo skin testing should receive carbapenems via graded challenge. (C)

There are no formal studies into the immunogenicity or frequency of allergic reactions to carbapenems. Evaluation of IgE-mediated allergy to carbapenems is analogous to that of cephalosporins and monobactams. No standardized skin test reagents are available, and skin testing with nonirritating concentrations of the native antibiotic has questionable predictive value.

The extent of clinical cross-reactivity between carbapenems and other  $\beta$ -lactams appears to be very low. Retrospective studies of hospitalized patients with a history of penicillin allergy (who were not skin tested) showed that approximately 10% developed possibly allergic reactions during treatment with carbapenems, and none of these reactions was life-threatening.<sup>453-455</sup> Among penicillin skin test–positive patients, 111 of 112 were skin test negative to imipenem and all 111 tolerated challenge with imipenem.<sup>26</sup> Similar tolerability was seen with meropenem in this same

group of individuals.<sup>25</sup> A previous study found that 20 of 40 penicillin skin test–positive patients were skin test positive to imipenemoyl-polylysine or imipenemoate, and none of them were challenged with imipenem.<sup>456</sup> Therefore, penicillin skin test–negative patients may safely receive carbapenems. Penicillin skin test–positive patients and patients with a history of penicillin allergy who do not undergo skin testing should receive carbapenems via graded challenge.

## B. Non- $\beta$ -Lactam Antibiotics

*Summary Statement 109:* Any non- $\beta$ -lactam antibiotic has the potential of causing an IgE-mediated reaction, but these appear to occur less commonly than with  $\beta$ -lactam antibiotics. (C)

*Summary Statement 110:* There are no validated diagnostic tests for evaluation of IgE-mediated allergy to non- $\beta$ -lactam antibiotics. (C) Evaluation of possible allergy to these antibiotics should be limited to situations when treatment with the drug is anticipated (rather than electively as for penicillin). (D)

*Summary Statement 111:* Skin testing with nonirritating concentrations of non- $\beta$ -lactam antibiotics is not standardized. A negative skin test result does not rule out the possibility of an immediate-type allergy. A positive skin test result suggests the presence of drug specific IgE antibodies, but the predictive value is unknown. (D)

*Summary Statement 112:* Patients with a history of reactions to non- $\beta$ -lactam antibiotics consistent with an IgE-mediated mechanism should only receive them if an alternate agent cannot be substituted and only via rapid induction of drug tolerance. (D)

*Summary Statement 113:* Sulfonamide antibiotics rarely cause IgE-mediated reactions and more commonly result in delayed maculopapular rashes, particularly in human immunodeficiency virus–positive patients. (C)

*Summary Statement 114:* There is no evidence to suggest allergic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides. (C)

*Summary Statement 115:* Vancomycin rarely causes IgE-mediated reactions, but more than 50% of patients experience immediate cutaneous erythema, flushing, and pruritus (red man syndrome), which is the result of non-IgE-mediated histamine release. (C)

*Summary Statement 116:* Red man syndrome reactions can be prevented by slowing the rate of infusion and premedicating with histamine<sub>1</sub> receptor antihistamines. (C)

*Summary Statement 117:* Aminoglycosides rarely cause drug allergic reactions, including IgE-mediated systemic reactions. (C)

*Summary Statement 118:* IgE-mediated and non-IgE-mediated anaphylactic reactions have been reported with quinolones. In vitro studies suggest a large extent of allergic cross-reactivity among quinolones, but there are no clinical studies to confirm this. (C)

*Summary Statement 119:* Anaphylactic or anaphylactoid reactions during the operative and perioperative periods may

Table 18. Nonirritating Concentrations of 15 Antibiotics<sup>428</sup>

Antimicrobial drug	Full-strength concentration	Dilution from full strength	Nonirritating concentration
Azithromycin	100 mg/mL	10 <sup>-4</sup>	10 μg/mL
Cefotaxime	100 mg/mL	10 <sup>-1</sup>	10 mg/mL
Cefuroxime	100 mg/mL	10 <sup>-1</sup>	10 mg/mL
Cefazolin	330 mg/mL	10 <sup>-1</sup>	33 mg/mL
Ceftazidime	100 mg/mL	10 <sup>-1</sup>	10 mg/mL
Ceftriaxone	100 mg/mL	10 <sup>-1</sup>	10 mg/mL
Clindamycin	150 mg/mL	10 <sup>-1</sup>	15 mg/mL
Cotrimoxazole	80 mg/mL	10 <sup>-2</sup>	800 μg/mL
Erythromycin	50 mg/mL	10 <sup>-3</sup>	50 μg/mL
Gentamicin	40 mg/mL	10 <sup>-1</sup>	4 mg/mL
Levofloxacin	25 mg/mL	10 <sup>-3</sup>	25 μg/mL
Nafcillin	250 mg/mL	10 <sup>-4</sup>	25 μg/mL
Ticarcillin	200 mg/mL	10 <sup>-1</sup>	20 mg/mL
Tobramycin	80 mg/2 mL	10 <sup>-1</sup>	4 mg/mL
Vancomycin	50 mg/mL	10 <sup>-4</sup>	5 μg/mL

be caused by induction agents, muscle relaxing agents, opiates, antibiotics, and latex allergy. (C)

Allergic reactions to non-β-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 trimethoprim-sulfamethoxazole, are more prone to induce such reactions, particularly in HIV-infected individuals (see section VII.F).<sup>457</sup> Because there are no validated diagnostic tests for allergies to non-β-lactam antibiotics, evaluation of a possible allergy should not be performed electively but rather be limited to situations when treatment with the drug is required and anticipated.

For most non-β-lactam antibiotics, there are case reports of positive skin test results 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. Although no validated *in vivo* or *in vitro* diagnostic tests are available for non-β-lactam antibiotics, skin testing with nonirritating concentrations of the drug (ie, negative skin test reactivity in a panel of normal, nonexposed volunteers) may provide useful information. Table 18 lists nonirritating concentrations for intradermal skin testing for 15 commonly used antibiotics. If the skin test result is positive under these circumstances, it is likely that drug specific IgE antibodies are present. Therefore, the patient should receive an alternative non-cross-reacting antibiotic or undergo rapid induction of drug tolerance. On the other hand, a negative skin test result does not denote that drug specific IgE antibodies are absent because it is possible that a drug metabolite not present in the test reagent may be the relevant allergen. However, if this particular antibiotic is required for treatment, the amount of drug injected intracutaneously can be used as the initial starting dose for rapid induction of drug tolerance. In skin test-negative patients who have mild reaction histo-

ries, a graded challenge procedure may be considered. Readministration of drugs that caused severe non-IgE-mediated reactions (such as SJS, TEN, and others), by either induction of drug tolerance or graded challenge, is generally contraindicated, with rare exceptions, such as treatment of a life-threatening infection in which case the benefit of treatment outweighs the risk of a potentially life-threatening reaction.

Up to 4% of patients treated with sulfonamide antibiotics experience allergic reactions.<sup>458</sup> The most typical reaction consists of a delayed maculopapular eruption, and type I reactions appear to be much less common. HIV-positive patients are at greatly increased risk of experiencing cutaneous reactions to trimethoprim-sulfamethoxazole, and this topic is discussed in more detail in section VII.F. There are data suggesting that patients with a history of allergy to sulfonamide antibiotics are at slightly increased risk of reacting to nonantibiotic sulfonamides, although this does not appear to be due to immunologic cross-reactivity but rather a nonspecific predisposition to react to drugs.<sup>27,459,460</sup> Although all sulfonamides contain an NH<sub>2</sub>-SO<sub>2</sub> moiety, sulfonamide antibiotics also contain an aromatic amine at the N<sub>4</sub> position and a substituted ring at the N<sub>1</sub> position, and these groups are believed to be essential for various types of allergic reactions to sulfonamide antibiotics.<sup>461-463</sup>

Vancomycin has been reported to cause drug fever, immune cytopenias, rash, or a distinctive cutaneous lesion, the red man syndrome, characterized by pruritus, erythema, and flushing of the face, neck, and upper chest with occasional hypotension. More than 50% of treated patients experience some of these manifestations, although most of them are mild. The symptoms are due to non-IgE-mediated histamine release that is probably related to the peak concentration,<sup>464</sup> so that slowing the rate of infusion will generally prevent further symptoms. Premedication with an histamine<sub>1</sub> receptor anti-histamine also helps to alleviate symptoms.<sup>465</sup> IgE-mediated anaphylaxis to vancomycin has also been observed and may be identified by skin tests, but skin tests at concentrations of 100 μg or greater may elicit false-positive wheal-and-flare reactions in normal skin.<sup>354</sup> Anaphylaxis should be managed in the same manner described for other non-β-lactam antibiotics. For patients for whom an alternate antibiotic cannot be used, successful rapid induction of drug tolerance for IgE-mediated hypersensitivity to vancomycin has been described.<sup>345,348,466,467</sup>

Although aminoglycosides rarely cause hypersensitivity reactions, there are individual case reports of IgE-mediated systemic reactions.<sup>468-470</sup> Rapid induction of drug tolerance may be indicated when the allergy is thought to involve IgE antibodies and no alternative antibiotic is available.<sup>468</sup> Both graded challenge and induction of drug tolerance procedures should be performed by specialists experienced with these protocols and the possible adverse events associated with them. The degree of allergic cross-reactivity among aminoglycosides is unknown but is assumed to be high.

Quinolones are a class of antibiotics related to nalidixic acid. Anaphylactoid reactions to this class of drug after the

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initial dose have been reported to occur at a rate of 1:1,000 and 1:100,000.<sup>471-473</sup> Reports of IgE-mediated anaphylactic reactions to quinolones appear to be increasing, possibly because of increased use of these agents.<sup>28-31</sup> In vitro studies suggest a large extent of allergic cross-reactivity among quinolones,<sup>2,28,29</sup> but there are no clinical studies to confirm this. Delayed cutaneous eruptions appear in approximately 2% of quinolone-treated patients.<sup>32,33</sup> There is evidence to show that drug-specific T cells are responsible for delayed maculopapular exanthems from quinolones.<sup>472</sup>

Although bacitracin is a common cause of type IV contact dermatitis reactions,<sup>474</sup> there are rare published reports of IgE-mediated anaphylactic reactions to bacitracin.<sup>475-477</sup>

### C. Antimycobacterial Drugs

*Summary Statement 120:* Allergic drug reactions to antimycobacterial drugs present significant problems in the implementation of long-term treatment regimens and preventing drug resistance to *Mycobacterium tuberculosis*. (C)

Shortly after the introduction of the first-line drugs (streptomycin and para-amino salicylic acid) as effective therapy for tuberculosis, it became apparent that these drugs can induce both minor and life-threatening allergic reactions.<sup>478-480</sup> The frequency of allergic reactions to streptomycin is still considerable when used alone or in combination with other agents.<sup>481,482</sup> Many allergic reactions were also encountered after use of second-generation drugs, including isoniazid, ethambutol, pyrazinamide, and rifampicin.<sup>34</sup> These include anaphylaxis, angioedema, pulmonary infiltrates, and cutaneous reactions.<sup>35-39</sup> Many cases of rifampicin-induced, non-IgE immune reactions present with a flulike syndrome with subsequent thrombocytopenia, hemolytic anemia, and renal failure.<sup>483</sup> A significant confounder is the fact that a relatively high occurrence (up to 1%) of toxic rather than allergic hepatitis may occur in the therapeutic course of isoniazid or rifampicin.<sup>34</sup> Occasionally, patients may develop hypersensitivity to multiple antimycobacterial drugs (eg, streptomycin, rifampicin, and ethambutol) either concurrent or sequential.<sup>34,481</sup>

In addition to the previously discussed multisystem syndrome, dapsone, the drug of choice in the treatment of leprosy and neutrophilic dermatoses, may rarely induce other immune-mediated reactions, such as rash DRESS, renal hypersensitivity vasculitis, angioedema, and/or interstitial pneumonitis.<sup>484-487</sup>

### D. Diabetes Medications

*Summary Statement 121:* The advent of human recombinant insulin has greatly reduced the incidence of life-threatening allergic reactions to approximately 1%. (C)

*Summary Statement 122:* Metformin and sulfonylurea antidiabetic drugs rarely cause immune-mediated reactions, such as leukocytoclastic vasculitis, generalized arteritis, granulomatous hepatitis, and autoimmune pemphigus vulgaris. (C)

Since the introduction of purified human recombinant insulin, allergy to insulin is rare and is now encountered in less

than 1% of patients.<sup>40-43</sup> However, life-threatening allergic reactions to human insulin and insulin analogs (Aspart, Lispro, and Glargine) have been documented and can be confirmed by appropriate intracutaneous and/or in vitro testing.<sup>44,45</sup> The latter tests have also revealed immunologic cross-reactivity to porcine and bovine insulin.<sup>488</sup> Tolerance to insulin may be achieved by continuous subcutaneous infusion of insulin lispro.<sup>489,490</sup> Adverse reactions to inhaled insulin have not been reported, but there is a marginally greater decline in pulmonary function tests in subjects with asthma or chronic obstructive pulmonary disease.<sup>491</sup> As has been the case for many years, protamine (ie, neutral Hagedorn insulin) may either masquerade as insulin allergy or act as a concurrent sensitizing drug.<sup>40,492</sup>

Leukocytoclastic vasculitis, generalized arteritis, granulomatous hepatitis, and autoimmune pemphigus vulgaris are rare immune-mediated reactions that have been described to occur during treatment with metformin and/or sulfonylurea antidiabetic agents.<sup>47-53</sup>

### E. Cancer Chemotherapeutic Agents

*Summary Statement 123:* Cancer chemotherapeutic agents, such as taxanes (paclitaxel, docetaxel), platinum compounds (cisplatin, carboplatin, oxaliplatin), and asparaginase, may cause severe immediate-type reactions, which may be either anaphylactic or anaphylactoid in nature. (C)

*Summary Statement 124:* For some chemotherapeutics (primarily the platinum-based compounds), skin testing may assist in identifying allergic patients who are at increased risk for an allergic reaction and for confirming IgE-mediated sensitivity. (C)

*Summary Statement 125:* Rapid induction of drug tolerance protocols are available for most chemotherapeutic agents that cause immediate-type reactions, but they are not uniformly successful. (C)

*Summary Statement 126:* Methotrexate can cause interstitial reactions in the lungs, which can progress to fibrosis if use of the drug is continued. (C)

Hypersensitivity reactions have been reported for virtually all commonly used chemotherapeutic agents. Reactions range from mild cutaneous eruptions to fatal anaphylaxis. In some cases, it is difficult to determine whether a reaction is anaphylactic (ie, mediated by drug specific IgE antibodies) or anaphylactoid (due to nonimmune degranulation of mast cells and basophils). Some reactions may be the result of excipients rather than the active drug, such as Cremophor-EL, a lipid solvent vehicle used in paclitaxel and other intravenous chemotherapeutics. Cremophor-EL is a nonionic emulsifier consisting of a mixture of amphiphilic molecules that form micelles, spherical "core-shell" structures. These Cremophor-EL particles in blood activate complement, leading to production of anaphylatoxins.<sup>493</sup>

In addition to life-threatening reactions, cancer chemotherapeutic agents (eg, cyclophosphamide, methotrexate) may induce a variety of cutaneous IgE and non-IgE allergic manifestations. These include urticaria, erythroderma, mixed cu-

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taneous dermatitides, leukocytoclastic vasculitis, and toxic epidermal necrolysis. The possibility of such reactions is particularly important when toxic drugs are used to treat immunologically mediated conditions such as vasculitis.

In the taxane family, paclitaxel and docetaxel produce anaphylactoid reactions in as many as 42% of patients on first administration,<sup>54</sup> suggesting an anaphylactoid mechanism. Pretreatment with systemic corticosteroids and antihistamines prevents the reaction in more than 90% of patients.<sup>55</sup> Patients who react despite pretreatment can usually be successfully desensitized.<sup>56,57</sup> Another option for patients who react to paclitaxel is to switch to docetaxel because most are able to tolerate it.<sup>59</sup>

Platinum compounds (cisplatin, carboplatin, and oxaliplatin) typically cause hypersensitivity reactions after completion of several treatment courses,<sup>60,61</sup> suggesting an immunologic mechanism. Pretreatment with corticosteroids and antihistamines does not prevent these reactions.<sup>62</sup> Skin testing with the undiluted drug has been found to identify patients at risk of reactions, and skin testing should be repeated before each subsequent course with the drug.<sup>61,63,64</sup> For patients with positive skin test results, various rapid induction of drug tolerance protocols have been reported, but they are not uniformly successful.<sup>61,63,64</sup> Immediate-type reactions to asparaginase occur in as many as 43% of patients, and the reaction rate increases after the fourth weekly dose.<sup>494</sup> It is unknown whether the mechanism is anaphylactic or anaphylactoid, and it may be different in different patients. Although use of skin testing with asparaginase before treatment has been recommended, it has not been shown to identify all patients at risk of reactions. Rapid induction of drug tolerance with asparaginase has been described.<sup>350</sup> In patients who react to *Escherichia coli* asparaginase, substitution of either *Erwinia* asparaginase or pegylated asparaginase may allow them to complete the treatment course.<sup>495,496</sup>

Methotrexate is a cause of noncytotoxic pulmonary reactions.<sup>65,66</sup> Methotrexate pneumonitis occurs most frequently within the first year of treatment, and the reported incidence of this reaction varies from 0.86% to 6.9%.<sup>67,68</sup> Symptoms of fever, cough, and dyspnea may occur anywhere from several days to several months after initiation of therapy. The chest radiograph is characterized by a diffuse, fine interstitial infiltrate. When use of 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 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>66,240</sup> Hypersensitivity pneumonitis in association with the use of an alkylating agent has also been documented.<sup>497</sup>

## F. HIV Medications

*Summary Statement 127:* Patients infected with HIV have an increased frequency of adverse reactions to a variety of drugs, and the pathogenesis of these reactions is likely multifactorial. (C)

*Summary Statement 128:* The most common adverse drug reaction in HIV-positive patients who take trimethoprim-sulfamethoxazole is a morbilliform and/or maculopapular eruption, often associated with fever that occurs after 7 to 12 days of therapy. (C)

*Summary Statement 129:* HIV-positive patients who have experienced typical delayed exanthematous reactions to trimethoprim-sulfamethoxazole and who require treatment with the drug (such as for *Pneumocystis jiroveci* pneumonia) may undergo one of several published trimethoprim-sulfamethoxazole induction of drug tolerance protocols. (D) Usually, this should be done after waiting for at least 1 month after the reaction to increase the likelihood of success. (D)

*Summary Statement 130:* Reintroduction of trimethoprim-sulfamethoxazole in HIV-positive patients with a history of more severe reactions to trimethoprim-sulfamethoxazole, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, is generally contraindicated, with rare exceptions, such as treatment of a life-threatening infection in which case the benefit of treatment outweighs the risk of a potentially life-threatening reaction. (D)

*Summary Statement 131:* Antiretroviral drugs used for highly active antiretroviral therapy (HAART) of HIV-infected patients may cause allergic reactions of various kinds. (C)

*Summary Statement 132:* Abacavir is the most common HAART drug to cause severe allergic reactions, and this risk is associated with the presence of HLA B 5701. (C)

Drug reactions are common in patients infected with HIV, and in some cases the incidence of reactions may be related to the degree of immunodeficiency.<sup>69-73</sup> These reactions cause significant morbidity and mortality in this population. The pathogenesis of adverse drug reactions in HIV-positive patients is unknown, but it is likely that the responsible mechanism is multifactorial.<sup>70</sup> Although these reactions are commonly referred to as being "allergic," it is likely that both toxic and immunologic mechanisms are involved. There are data to support several risk factors for the development of adverse drug reactions in HIV-positive patients. These include coexistent cytomegalovirus or Epstein-Barr virus infections, altered drug metabolism, slow acetylator phenotype, relative deficiency of glutathione or other scavengers, increased expression of major histocompatibility complex class I and II on keratinocytes, and high-dose trimethoprim-sulfamethoxazole treatment.<sup>298,498-504</sup>

Adverse reactions to sulfonamides may complicate both treatment and prophylaxis of *Pneumocystis jiroveci* pneumonia in many patients with AIDS. However, unlike reactions to amoxicillin<sup>505</sup> and antimycobacterial agents,<sup>506</sup> adverse reactions to sulfonamides may decrease with HIV disease progression.<sup>72</sup> Adverse cutaneous sulfonamide reactions may be tolerated without ceasing therapy in some cases. The use of 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 less than 500/ $\mu$ L, (3) hypotension, (4) dyspnea, or (5) any signs of

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blistering, desquamation of the skin, or mucous membrane involvement.

There appears to be a relationship between the development of adverse sulfonamide reactions and the dose administered because some patients can continue treatment after interruption of therapy or lowering of the dosage.<sup>499</sup> The degree of clinical cross-sensitivity among different sulfonamides is not known. The degree of clinical cross-sensitivity between trimethoprim-sulfamethoxazole and dapsone is thought to be low, and it appears that most patients who react to trimethoprim-sulfamethoxazole tolerate dapsone.<sup>507</sup> Dapsone, however, probably should not be used in those patients in whom trimethoprim-sulfamethoxazole caused severe reactions, such as SJS, or visceral involvement, such as hepatitis or pneumonitis.

The most common reaction to sulfonamides is a morbilliform, maculopapular eruption often associated with fever that occurs after 7 to 12 days of therapy. Immediate (anaphylaxis, urticaria/angioedema) and delayed (erythema multiforme minor, erythema multiforme major/SJS, TEN) hepatic, hematologic, renal, and immune complex reactions may occur. The spectrum of clinical manifestations of sulfonamide reactions in patients with AIDS suggests that most of these reactions are not IgE mediated. In addition, the observation that induction of drug tolerance protocols beginning with relatively high starting doses are often successful lends further support to the impression that an alternative pathogenic mechanism is operative. Sulfonamide specific IgG and IgM antibodies have been found in patients with AIDS, both those with and without skin reactions to sulfonamides.<sup>508,509</sup> It is unlikely that these antibodies play a pathogenic role in sulfonamide hypersensitivity reactions. For HIV-positive individuals who develop typical delayed maculopapular rashes after trimethoprim-sulfamethoxazole administration, many different induction of drug tolerance protocols have been developed and used successfully.<sup>74-85</sup> Reintroduction of trimethoprim-sulfamethoxazole by 1 of these protocols optimally should not take place any earlier than 1 month after the initial adverse reaction, and none of these protocols should be used in individuals with a history of bullous dermatitis or SJS. However, it may be started earlier if treatment of a serious infection requiring these drugs is necessary. Although reintroduction of trimethoprim-sulfamethoxazole in HIV-positive patients with a history of more severe reactions to trimethoprim-sulfamethoxazole, such as SJS is generally contraindicated, successful trimethoprim-sulfamethoxazole desensitization has been described in 2 patients with a history of SJS.<sup>510</sup> This should be considered only if alternate therapy has failed and the patient has a life-threatening infection, in which case benefit of treatment with trimethoprim-sulfamethoxazole outweighs the risk of a potentially life-threatening reaction.

It is not clear how or to what extent the immune response to trimethoprim-sulfamethoxazole is modified during these types of induction of drug tolerance procedures. In a randomized trial of trimethoprim-sulfamethoxazole induction of drug

tolerance vs rechallenge (single dose), the success rates were 79% and 72%, respectively, and the difference was not statistically significant.<sup>83</sup> Sulfadiazine, acyclovir, zidovudine, dapsone, and pentamidine induction of drug tolerance protocols have also been developed for patients with AIDS.<sup>86-91</sup>

In addition to trimethoprim-sulfamethoxazole, patients with AIDS may have an increased frequency of various drug allergic reactions and syndromes to a number of other agents, including antituberculous agents, pentamidine, amoxicillin-clavulanic acid, clindamycin, carbamazepine, phenytoin, thalidomide, foscarnet, and ciprofloxacin.<sup>505,506,511-514</sup> The fact that these reactions are clinically diverse suggests that they are likely produced by a variety of mechanisms.

Twenty antiretroviral drugs are approved by the US Food and Drug Administration for HAART of HIV-infected patients.<sup>92,93</sup> Many of these drugs have been associated with hypersensitivity responses ranging from mild cutaneous rashes to life-threatening SJS and TEN.<sup>94</sup> The most common HAART offenders are abacavir, all nonnucleoside reverse transcriptase inhibitors, and amprenavir.<sup>93</sup> Abacavir, a nucleoside analogue reverse transcriptase inhibitor, causes severe hypersensitivity in 4% to 5% of patients.<sup>95,96</sup> Such reactions have been identified with a genetic risk factor, the presence of HLA B 5701.<sup>97,98</sup> Among the nonnucleoside reverse transcriptase inhibitors, nevirapine has been cited most often as a cause of rash or combination of symptoms of fever, rash, and hepatitis.<sup>515</sup> This drug has been associated with an interaction between HLA-DRB1\*0101 and CD4<sup>+</sup> T cells higher than 250 cells/ $\mu$ L.<sup>516</sup> Women are at increased risk for nevirapine and other HAART-induced drug reactions.<sup>515</sup>

Coadministration of tuberculosis drugs and antiretroviral therapy in AIDS patients infected with *Mycoplasma hominis* and atypical organisms (*Mycobacterium avium*, *Mycobacterium intracellulare*) is often required. This combination is associated with 3 major complications: (1) induction of cytochrome P450 enzymes by rifampicin induces reduction of antiretroviral drug levels, (2) overlapping toxic effects and hypersensitivities occur often, and (3) an immunologic reaction termed "the immune reconstitution inflammatory syndrome" may develop.<sup>517</sup> It is postulated that increased risk of anaphylaxis is due to a skewing of T<sub>H</sub>2 cytokine cytokines.<sup>518</sup> Severe cutaneous hypersensitivity reactions, anaphylaxis, fulminant hepatitis, and SJS have been reported.<sup>37,519,520</sup>

## G. Disease-Modifying Antirheumatic Drugs (DMARDs)

*Summary Statement 133:* Apart from adverse reactions to aspirin, other NSAIDs, and certain pyrazolone derivatives (discussed in VII-R), a variety of allergic reactions to other DMARDs may occur. (C)

Parenteral gold salts were responsible for isolated instances of anaphylaxis, hypersensitivity pneumonitis, and severe mucocutaneous reactions.<sup>521-524</sup> D-penicillamine has been noted to induce bullous dermatoses and autoimmune diseases.<sup>525</sup> The potentially serious immunotoxic effects of methotrexate have been previously discussed. Combination therapy with azathioprine may lead to leukocytoclastic vasculitis in ap-

proximately 10% of such treatments.<sup>526</sup> Hydroxychloroquine is rarely associated with phototoxic and photoallergic dermatitis.<sup>527</sup> Sulfasalazine-induced reactions include DRESS and extrinsic allergic alveolitis.<sup>237,528</sup> Allergic reactions also occur after use of the newest DMARD, leflunomide. These include erythema multiforme, lupus erythematosus, and TEN.<sup>529-531</sup> Infusion reactions, frank allergic reactions, and new autoantibodies have been observed after treatment by anakinra, an interleukin 1 receptor antagonist.<sup>532,533</sup>

## H. Immunomodulatory Agents for Autoimmune Diseases

*Summary Statement 134:* Although hypersensitivity reactions to several unique therapeutic agents for autoimmune diseases have already occurred, it is too early to assess the global impact of adverse events for diverse immunologic interventions in early development. (C)

Glatiramer acetate (Copaxone) was developed as a copolymer with a mixture of amino acids resembling those of myelin basic protein to diminish the rate of relapse in multiple sclerosis.<sup>534</sup> Hypersensitivity reactions in the form of injection site and erythema nodosum have occurred<sup>535,536</sup>; instances of systemic reactions and anaphylaxis have been reported.<sup>537,538</sup> On the basis of a similar rationale, altered peptide ligands were evaluated in several phase 2 trials.<sup>539</sup> Although the efficacy results were promising, anaphylactic reactions to the self-peptide were encountered. Skin reactions are common after the use of interferon beta-1b.<sup>540</sup>

The immunologic complexity of systemic lupus erythematosus provides multiple therapeutic targets and corresponding therapies: B cells (rituximab), T- and B-cell collaboration (CTLA4Ig), B-cell factors (anti-BLyS, anti-BAFF), complement (anti-C5a antibodies), and suppressor proteins (suppressor of cytokine signaling-1).<sup>541</sup> Thus far, only rituximab has received significant clinical experience, and reactions to this agent will be discussed in section VII. T.<sup>186</sup> However, as some of the other biologic modifiers become part of the clinical armamentarium within the next few years, the possibility of allergic reactions to other new agents may be anticipated.

Immunomodulation strategies are being actively pursued for prevention or attenuation of type 1 diabetes. Thus far, most of these interventions are not autoantigen/HLA specific. Among the most promising of these immunotolerance interventions are (1)  $\beta$ -chain of insulin in incomplete Freund adjuvant, (2) an altered insulin peptide, (3) an alum-formulated glucose acid decarboxylase epitope, (4) rituximab, (5) CTLA-4 immunoglobulin, (6) anti-CD40L monoclonal antibody, and (7) anti-CD3 (anti-T-cell) monoclonal antibodies.<sup>542-544</sup> It is uncertain whether use of adjuvants (incomplete Freund adjuvant or alum) will counteract IgE-mediated reactions. As previously discussed, human monoclonal antibodies differ with respect to allergic effects, so it is not yet known how widespread use of anti-CD3 will fare in this respect, but a recent clinical trial showed promise.<sup>545,546</sup>

## I. Modifying Drugs for Dermatologic Diseases

*Summary Statement 135:* Allergic reactions to immunosuppressant and anti-inflammatory drugs are commonly encountered in the treatment of chronic cutaneous diseases. (C)

The modern dermatologic armamentarium consists of a spectrum of T-cell immunosuppressant drugs, such as macrolides (cyclosporine, tacrolimus, pimecrolimus, sirolimus), dapsone, mycophenolate mofetil, and previously discussed monoclonal antibodies. The macrolide immunosuppressants, which are extensively used to prevent transplantation rejection and to treat inflammatory bowel disease, are also used to treat psoriasis, a T<sub>H</sub>1-cytokine-mediated disease. In general, immune-mediated reactions to these agents are rare. Infusion reactions to cyclosporine have been attributed to an IgE-mediated reaction to the Cremophor-EL solvent. Although ingestion of cyclosporine is often tolerated after such severe events, anaphylactic shock has also rarely occurred after oral cyclosporine.<sup>547-550</sup> Angioedema and leukocytoclastic vasculitis have been reported after use of tacrolimus and sirolimus, respectively.<sup>551-554</sup> Both cyclosporine and tacrolimus may be associated with elevated total IgE levels.<sup>555,556</sup> In the case of tacrolimus, food and inhalant specific IgE levels were also elevated, and several children developed clinical food allergies, suggesting that these agents may induce a shift to a T<sub>H</sub>2 pattern.<sup>552,554,556</sup> Apart from its toxic effects of methemoglobinemia, hemolytic anemia, and previously discussed hypersensitivity effects, dapsone may induce a potentially fatal multisystem disorder known as the dapsone hypersensitivity syndrome.<sup>557,558</sup> Urticaria and a severe papulosquamous skin eruption have been reported after use of CellCept (mycophenolate mofetil).<sup>559,560</sup> Of particular interest to allergists is the fact that all of these drugs have been and are being used for the treatment of refractory atopic dermatitis or chronic idiopathic urticaria.<sup>561-564</sup>

## J. Perioperative Agents

*Summary Statement 136:* Anaphylactic or anaphylactoid reactions during the operative and perioperative periods may be caused by induction agents, muscle-relaxing agents, opiates, antibiotics, and latex allergy. (C)

Anaphylactic or anaphylactoid reactions are not infrequent during general anesthesia.<sup>565</sup> The incidence of these reactions during general anesthesia is estimated to be between 1 in 2,100 to 1 in 20,000 anesthetics.<sup>565,566</sup> The higher incidence (1 per 2,100 operations) was reported in a 12-year French pediatric survey.<sup>566</sup> The reactions may be due to induction agents, neuromuscular blocking agents, antibiotics, opiates, and latex. Because anaphylactic reactions cannot be distinguished from anaphylactoid, nonimmune occurrences, it has been recommended that plasma histamine, tryptase, and specific IgEs (if available) may be ordered at the time of reaction and skin tests be performed later.<sup>99</sup> The incidence of life-threatening reactions to muscle relaxants has been estimated at 1 in 4,500 anesthesia events.<sup>567</sup> Some muscle relaxants, such as curare, are potent histamine-releasing agents.<sup>568,569</sup> Others, such as atracurium, pancuronium, and vecuronium,

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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 1 mechanism.<sup>570</sup> Life-threatening reactions to propofol, which is formulated with soybean oil, egg phosphatide, and sometimes metabisulfite, have been reported.<sup>571-573</sup> Hyaluronidase in ophthalmic anesthesia may cause angioedema.<sup>574</sup> The diagnosis and management of reactions occurring during and after surgery are discussed in more detail in the Anaphylaxis Practice Parameter<sup>326</sup> and Diagnostic Testing Practice Parameter.<sup>330</sup>

### K. Blood and Blood Products

*Summary Statement 137:* Reactions due to blood and blood products include urticaria, anaphylaxis (particularly in patients with complete IgA deficiency), anaphylactoid reactions, and transfusion-related acute lung injury (TRALI). (C)

Acute urticarial reactions occur in 1% to 3% of blood transfusions, whereas significant bronchoconstriction/laryngeal edema and anaphylactic shock occur in 0.1% to 0.2% and 0.002% to 0.005%, respectively.<sup>575</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>576,577</sup> Activation of complement and other non-IgE-mediated reactions may also occur after blood transfusions, presumably as a result of alloantigenic reactivity.<sup>575</sup> Reactions to human serum albumin are extremely rare (0.01%), but occasionally allergic patients exhibit positive prick test results to albumin-containing diluent solutions.<sup>578</sup> Such reactivity has been demonstrated in house dust mite-sensitive patients tested with mite culture medium containing human serum albumin components. TRALI is a complex syndrome that has multiorgan manifestations and has only recently been identified to be an important cause of transfusion-associated morbidity and mortality.<sup>104,105</sup> The pathogenesis of TRALI is as yet unknown, but it is postulated to involve (1) an antibody-mediated event caused by transfusion of donor antibodies (anti-HLA or antigranulocytic) into patients whose leukocytes express the cognate antigen and/or (2) pulmonary endothelial activation leading to endothelial damage and capillary leak syndrome after the transfusion.<sup>579</sup>

### L. Opiates

*Summary Statement 138:* Opiates and their analogs are a common cause of pseudoallergic reactions that are generally mild, are not life-threatening, and can be attenuated by preadministration of histamine<sub>1</sub> receptor antihistamines. (C)

Opiates such as morphine, meperidine, codeine, and narcotic analogs can stimulate mast cell-mediated release directly without a specific immunologic mechanism. Patients who exhibit this tendency may experience generalized pruritus and urticaria after administration of a narcotic analgesic. Occasional mild wheezing may be noted. Skin test results to

opiates are difficult to interpret because these agents cause release of histamine from skin mast cells in all patients. Dilute skin test concentrations have been recommended if an IgE-mediated reaction is suspected.<sup>580</sup> A single case of a documented IgE-mediated reaction to morphine has been reported.<sup>581</sup> Some opiate reactions can be attenuated by preadministration of antihistamines. Narcotic-induced pseudoallergic reactions are rarely life-threatening. If there is a history of such a reaction to an opiate and analgesia is required, a nonnarcotic 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.

### M. Corticosteroids

*Summary Statement 139:* Immediate-type reactions to corticosteroids are rare and may be either anaphylactic or anaphylactoid in nature. (C)

*Summary Statement 140:* Most reported reactions to corticosteroids involved intravenous methylprednisolone and hydrocortisone, and preservatives and diluents have also been implicated. (C)

Allergic contact dermatitis (Gell-Coombs type IV reaction) due to topical application of corticosteroids is the most common type of allergic reaction induced by this class of drugs. Rarely, immediate-type allergic reactions to corticosteroids have been described. Most such reported reactions are due to intravenous administration of methylprednisolone and hydrocortisone.<sup>53,106-111</sup> Patients with AERD or renal transplants may be at increased risk of reacting to corticosteroids, but this could be due to increased use of corticosteroids in these patients. In most cases, drug specific IgE has not been detected (either via skin testing or in vitro tests). Hence, it is unclear whether these reactions are anaphylactoid or represent true IgE-mediated allergy. Some of the reactions are believed to be secondary to the diluent or preservative, rather than the active drug.<sup>107,296</sup> Although corticosteroid-induced reactions are rare, the possibility should be entertained in patients who experience immediate symptoms (urticaria, angioedema, bronchospasm) in the context of receiving the drug, with no other ascertained cause. Evaluation should include skin testing with the corticosteroid in question, although its predictive value is uncertain. Skin testing with the diluent itself may also be helpful. Because most (but not all) patients appear to be able to tolerate other corticosteroids, management should focus on finding an alternate agent for future use. If a patient with suspected allergy to a corticosteroid requires treatment with it, rapid induction of drug tolerance should be performed.

### N. Protamine

*Summary Statement 141:* Severe immediate reactions may occur in patients receiving protamine for reversal of heparinization. (C)

*Summary Statement 142:* Diabetic patients receiving protamine-containing insulin are at greatest risk of severe reactions due to intravenous protamine. (C)

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Protamine sulfate is a low-molecular-weight (4500 Da) polycationic protein isolated from salmon testes. Its original use was to complex insulin (neutral protamine Hagedorn [NPH] insulin) to delay absorption, but it is also used to reverse the anticoagulant effects of heparin after a variety of procedures, including cardiopulmonary bypass and hemodialysis. Immediate generalized reactions to protamine, including hypotension, shock, and death, have been reported.<sup>100,101</sup> The occurrence of dose-dependent hypotension after rapid intravenous administration may be a manifestation of non-specific histamine release.<sup>582</sup> However, the fact 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>102,103</sup> IgE and IgG antibodies directed against protamine have been detected in some patients who reacted to protamine.<sup>100</sup> IgE-mediated reactions to the protamine moiety of NPH insulin also have been reported.<sup>583</sup> There are no widely available alternate agents for heparin reversal. Pretreatment with corticosteroids and antihistamines has been recommended, but no studies have shown this to be efficacious.

#### O. Heparin

*Summary Statement 143:* Hypersensitivity reactions to unfractionated heparin and low-molecular-weight heparin are uncommon and include thrombocytopenia, various cutaneous eruptions, hypereosinophilia, and anaphylaxis. (C)

Hypersensitivity reactions to unfractionated heparin and low-molecular-weight heparin are uncommon and include thrombocytopenia, various cutaneous eruptions, hypereosinophilia, and anaphylaxis. Mild thrombocytopenia is due to platelet aggregation and occurs in 1% to 3% of patients treated with unfractionated heparin. Severe thrombocytopenia is caused by immune complexes, a component of which is heparin-dependent IgG specific for platelet factor 4.<sup>112</sup> This reaction usually occurs after approximately 5 days of treatment with unfractionated heparin and is associated with development of thrombosis and necrosis. Low-molecular-weight heparin does not cause anti-platelet 4 IgG-related reactions, but it may cause thrombocytopenia. Although immediate hypersensitivity reactions to unfractionated heparin and low-molecular-weight heparin are rare, anaphylactic and anaphylactoid reactions have been documented.<sup>584,585</sup> The extent of allergic cross-reactivity between high- and low-molecular-weight heparins is unknown.<sup>586,587</sup> Management of patients with allergic reactions to heparin may require switching to a direct thrombin inhibitor such as a hepanoid (danaparoid) or a hirudin (lepirudin or argatroban). However, patients may develop antihirudin antibodies, and a small percentage of such patients may experience anaphylaxis.<sup>588</sup> A recent outbreak of anaphylactic reactions to heparin in the United States and Germany was attributed to a contaminant in heparin lots, an oversulfated form of chondroitin sulfate. This oversulfated chondroitin sulfate contaminant has been shown in vitro and in vivo to cause activation of the kinin-kallikrein

pathway with generation of bradykinin, a potent vasoactive mediator, and generation of C3a and C5a anaphylatoxins.<sup>113</sup> Clinically, reactions to contaminated heparin products were associated with hypotension and abdominal pain, and variably angioedema, but typically lacked urticaria and pruritus.<sup>114</sup> The findings of abdominal pain and angioedema are somewhat analogous to C1 inhibitor deficiency in which symptoms are due to local production of bradykinin.

#### P. Local Anesthetics

*Summary Statement 144:* Most adverse reactions to local anesthetics are not due to IgE-mediated mechanisms but are due to nonallergic factors that include vasovagal responses, anxiety, toxic reactions including dysrhythmias, and toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine effects. (C)

*Summary Statement 145:* To exclude the rare possibility of an IgE-mediated reaction to local anesthetics, skin testing and graded challenge can be performed in patients who present with a reaction history suggestive of possible IgE-mediated allergy to these drugs. (B)

Possible systemic allergy to local anesthetics is often of concern to patients and their dentists or physicians. Documentation of IgE-mediated reactions is extremely rare.<sup>115-118</sup> Most adverse reactions to local anesthetics are due to nonallergic factors that include vasovagal responses, toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine, or anxiety.<sup>589-592</sup> Of these, anxiety is probably the most difficult to manage. Therefore, the history of a previous reaction must be carefully evaluated. It is necessary to determine the type of local anesthetics to be used. Local anesthetics are either group 1 benzoic acid esters (eg, procaine, benzocaine) or group 2 amides (eg, lidocaine, mepivacaine). On the basis of patch testing, the benzoic acid esters cross-react with each other, but they do not cross-react with the group 2 amide drugs. It is not known what, if any, relevance this has on immediate-type reactions to local anesthetics. Graded challenge tests may then be performed using incremental concentrations of the local anesthetic that the dentist intends to use. This test reagent should not contain epinephrine or other additives, such as parabens or sulfites. When there is concern about a previously reported reaction, skin testing and incremental challenge with a local anesthetic is a reasonable approach in the evaluation of a possible reaction. Although there are slight differences in reported graded challenge procedures, a typical protocol is as follows. Skin prick tests are first performed with the undiluted anesthetic. If the result 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. A placebo step may be added after the skin prick test and before challenging with the local anesthetic. With this protocol, there have been no serious allergic reactions reported after administration of local anesthetics if the skin test results and test dosing are negative.<sup>591</sup>

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A more recent evaluation of a similar protocol revealed no incidence of an allergic reaction in a total of 256 referred patients.<sup>593</sup> Test reagents in this investigation included preservatives and epinephrine. The investigators concluded that local anesthetic tests could be performed with formulations that contain either preservatives and/or epinephrine.

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) that is least likely to produce a reaction.

False-positive intracutaneous test results may occur in some history-negative patients and patients with a history of adverse reactions to local anesthetics.<sup>594</sup> On the basis of the low pretest probability of IgE-mediated local anesthetic allergy and the occurrence of false-positive results, it is unclear whether intracutaneous tests have any benefit in the diagnostic approach to local anesthetic allergy.<sup>593</sup> Rare patients may also have positive skin test results to methylparabens in the local anesthetics, and some of these may be false-positive skin test results because subsequent results of subcutaneous challenges to local anesthetic with methylparabens are negative.<sup>595</sup> Subcutaneous local anesthetic challenges using a graded incremental approach after skin tests have been reported to be a safe method in a study of 236 patients with histories of adverse reactions to local anesthetics.<sup>593</sup> Alternatively, a more rapid subcutaneous challenge approach using 1.0 mL of saline (placebo) followed in 20 minutes by 1.0 mL of undiluted local anesthetic was a safe and effective method in a study of 252 patients.<sup>595</sup>

#### **Q. Radiocontrast Media (RCM)**

*Summary Statement 146:* Anaphylactoid reactions occur in approximately 1% to 3% of patients who receive ionic RCM and less than 0.5% of patients who receive nonionic RCM. (C)

*Summary Statement 147:* Risk factors for anaphylactoid reactions to RCM include female sex, atopy, concomitant use of  $\beta$ -blocking drugs, and a history of previous reactions to RCM. (C)

*Summary Statement 148:* Although asthma is associated with an increased risk of a RCM reaction, specific sensitivity to seafood (which is mediated by IgE directed to proteins) does not further increase this risk. There is no evidence that sensitivity to iodine predisposes patients to RCM reactions. (C)

*Summary Statement 149:* Patients who experienced previous anaphylactoid reactions to RCM should receive nonionic, iso-osmolar agents and be treated with a premedication regimen, including systemic corticosteroids and histamine<sub>1</sub> receptor antihistamines; this will significantly reduce, but not eliminate, risk for anaphylactoid reaction with reexposure to contrast material. (D)

*Summary Statement 150:* Delayed reactions to RCM, defined as reactions occurring 1 hour to 1 week after administration, occur in approximately 2% patients. (C) Most are

mild, self-limited cutaneous eruptions that appear to be T-cell mediated, although more serious reactions, such as SJS, TEN, and DRESS syndrome, have been described.

Adverse reactions to RCM are classified as chemotoxic or anaphylactoid. Chemotoxic reactions (cardiotoxicity, neurotoxicity, and nephrotoxicity) are related to the chemical properties of the contrast agent, and they are dose and concentration dependent. Chemotoxic reactions tend to occur in medically unstable patients who are debilitated. Anaphylactoid reactions occur in approximately 1% to 3% of patients who receive ionic RCM and less than 0.5% of patients who receive nonionic agents.<sup>119,120</sup> Severe life-threatening reactions are less common, occurring in 0.22% of patients receiving ionic RCM and 0.04% of patients receiving nonionic agents.<sup>121</sup> The fatality rate from RCM is approximately 1 to 2 per 100,000 procedures, and it is similar for both ionic and nonionic agents.<sup>596,597</sup> Risk factors for anaphylactoid reactions to RCM include female sex, asthma, and a history of previous anaphylactoid reaction to RCM;  $\beta$ -blocker exposure and/or presence of cardiovascular conditions is associated with greater risk for more serious anaphylactoid reaction.<sup>122-126</sup>

A relationship between anaphylactoid reaction to RCM and “seafood allergy” is a frequent misconception. There is no convincing evidence in the medical literature that individuals with “seafood allergy” are at elevated risk for anaphylactoid reaction to RCM compared with the general population. The pathogenesis of anaphylactoid reactions is also unrelated to iodine. Rates of anaphylactoid reactions to low-osmolar contrast agents are significantly lower than rates observed with conventional contrast media,<sup>121</sup> yet their content of iodine is similar. RCM reactions are typically not mediated by specific IgE antibodies with rare exceptions.<sup>598</sup> RCM likely has direct effects on mast cells and basophils, leading to degranulation and systemic mediator release, which accounts for the clinical manifestations of anaphylactoid reactions. Complement activation may account for some reactions.

Management of a patient who requires RCM and has had a prior anaphylactoid reaction to RCM includes the following: (1) determine whether the study is essential; (2) determine that the patient understands the risks; (3) ensure proper hydration; (4) use a nonionic, iso-osmolar RCM, especially in high-risk patients (asthmatic patients, patients taking  $\beta$ -blockers, and those with cardiovascular disease), and (5) use a pretreatment regimen that has been documented to be successful in preventing most reactions.<sup>127-130</sup> One reported regimen consists of prednisone, 50 mg, at 13, 7, and 1 hour before the procedure; diphenhydramine, 50 mg, at 1 hour before the procedure; and either ephedrine, 25 mg, or albuterol, 4 mg, at 1 hour before the procedure. However, the latter agents may not be favorable from a risk-benefit standpoint in patients with cardiovascular disease. Although histamine<sub>2</sub> receptor antagonists are beneficial in the treatment of anaphylaxis,<sup>326</sup> when the addition of histamine<sub>2</sub> receptor antagonists 1 hour before RCM procedures was studied, paradoxically, a modest increase in reaction rate was observed.<sup>127</sup>

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Delayed reactions to RCM, defined as those occurring between 1 hour and 1 week after administration, occur in approximately 2% of patients.<sup>131</sup> These reactions most commonly manifest as mild, self-limited cutaneous eruptions and do not require any treatment.<sup>131</sup> The mechanism of delayed skin reactions to RCM appears to be T-cell mediated.<sup>132</sup> Rarely, more serious and life-threatening delayed reactions to RCM have been described, such as SJS, TEN, and DRESS.<sup>599</sup>

## **R. Aspirin and Nonsteroidal Anti-inflammatory Agents (NSAIDs)**

*Summary Statement 151:* One type of adverse reaction to aspirin and NSAIDs is AERD, a clinical entity characterized by aspirin- and NSAID-induced respiratory reactions in patients with underlying asthma and/or rhinitis or sinusitis. (B)

*Summary Statement 152:* The mechanism of AERD appears to be related to aberrant arachidonic acid metabolism. (B)

*Summary Statement 153:* Controlled oral provocation with aspirin is considered to be the most conclusive way to confirm the diagnosis of AERD. (B)

*Summary Statement 154:* Aspirin and NSAIDs that inhibit cyclooxygenase 1 (COX-1) cross-react and cause respiratory reactions in AERD, whereas selective COX-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely. (B)

*Summary Statement 155:* Aspirin desensitization followed by daily aspirin therapy to perpetuate the aspirin tolerant state in patients with AERD is indicated in patients with AERD if aspirin or NSAIDs are therapeutically necessary for treatment of some other condition, such as cardiac or rheumatologic diseases. (D)

*Summary Statement 156:* Aspirin desensitization followed by daily aspirin has been associated with improved outcomes in patients with AERD who are poorly controlled with medical and/or surgical management. (D)

*Summary Statement 157:* A second reaction type to aspirin and NSAIDs is exacerbation of urticaria and angioedema in approximately 20% to 40% of patients with underlying chronic idiopathic urticaria. (C) Drugs that inhibit COX-1 cross-react to cause this reaction, whereas selective COX-2 inhibitors typically are better tolerated by these patients. (C)

*Summary Statement 158:* A third reaction type to aspirin and NSAIDs is suggestive of an IgE-mediated mechanism and manifests as urticaria or angioedema or anaphylaxis, and it occurs in patients with no underlying respiratory or cutaneous disease. (C) These reactions appear to be drug specific and there is no cross-reactivity with other NSAIDs. (D)

*Summary Statement 159:* A fourth reaction type to aspirin and NSAIDs is urticaria or angioedema caused by all drugs that inhibit COX-1, and it occurs in patients without a prior history of chronic urticaria. (C)

*Summary Statement 160:* Rarely, patients exhibit combined ("blended") respiratory and cutaneous reaction to aspirin or NSAIDs and hence cannot be classified into 1 the 4 reaction types described above. (C)

Aspirin and NSAIDs can cause a spectrum of drug allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis. AERD is a clinical entity characterized by aspirin- and NSAID-induced respiratory reactions in patients with chronic rhinosinusitis and asthma. The nomenclature ascribed to this type of reaction has included terms such as *aspirin sensitivity*, *aspirin intolerance*, *aspirin idiosyncrasy*, *aspirin-induced asthma*, and *aspirin triad*.<sup>600</sup> AERD does not fit precisely into a specific category of adverse drug reactions. AERD typically follows an illness and starts as severe perennial rhinitis followed by the development of nasal and/or sinus polyps, which then progress to include symptoms of asthma.<sup>140</sup> Rhinitis is often complicated by chronic sinusitis, anosmia, and nasal polyposis. Asthma and sensitivity to aspirin usually develop several years after the onset of rhinitis. Upper and lower respiratory tract symptoms are frequently sudden and severe after administration of aspirin or any NSAID that inhibits the COX-1 enzyme. Despite avoidance of aspirin and cross-reacting drugs, these patients typically experience refractory rhinosinusitis and asthma—in some cases requiring repeated sinus surgery procedures and regular administration of oral steroids. AERD is rare in asthmatic children and becomes increasingly more common in adults with asthma. Approximately 10% of adults with asthma and a third of patients with asthma with nasal polyposis have AERD.<sup>601</sup>

The mechanism of AERD is related to aberrant arachidonic acid metabolism. Before administration of aspirin, compared with non-aspirin-sensitive asthmatic patients, patients with AERD have higher levels of both COX and 5-lipoxygenase products, such as increased urinary leukotriene E<sub>4</sub> and thromboxane B<sub>2</sub>, and increased leukotriene E<sub>4</sub> and thromboxane B<sub>2</sub> in bronchoalveolar lavage fluid.<sup>602-604</sup> Patients with AERD also have increased respiratory tract expression of the cysteinyl leukotriene 1 receptor and heightened responsiveness to inhaled leukotriene E<sub>4</sub>.<sup>133,134</sup> A number of genetic polymorphisms involving the leukotriene pathway have been reported to be associated with AERD, including the leukotriene C<sub>4</sub> promotor,<sup>605</sup> cysteinyl leukotriene receptor 1 promotor,<sup>606</sup> prostanoid receptor related genes,<sup>607</sup> and thromboxane A<sub>2</sub> receptor genes.<sup>608</sup> However, not all of these findings have been replicated, and there is significant heterogeneity in study populations (ie, Polish vs Korean populations).<sup>609</sup>

Administration of aspirin leads to inhibition of COX-1 with resultant decrease in prostaglandin E<sub>2</sub>. Prostaglandin E<sub>2</sub> normally inhibits 5-lipoxygenase, but with a loss of this modifying effect, arachidonic acid molecules are preferentially metabolized in the 5-lipoxygenase pathway, resulting in increased production of cysteinyl leukotrienes. After aspirin challenge, patients with AERD have elevated levels of urinary leukotriene E<sub>4</sub>, increased levels of histamine and leukotriene C<sub>4</sub> in nasal and bronchial secretions, and greatly up-regulated cysteinyl leukotriene receptors.<sup>602-604,610</sup> Tryptase and histamine are released into peripheral blood after aspirin administration, suggesting mast cell involvement.

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Aspirin and NSAIDs that inhibit COX-1 all cross-react and cause reactions in AERD. Analgesics that are poor inhibitors of COX-1 (eg, nonacetylated salicylates and acetaminophen) may cause reactions only if administered at high doses.<sup>611</sup> NSAIDs that preferentially inhibit COX-2 but also inhibit COX-1 at higher doses may result in reactions, depending on the dose given. Selective COX-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely.<sup>135-139</sup>

There is no diagnostic in vitro or skin test for AERD. The diagnosis is usually established by history, but if the history is unclear or when definite diagnosis is required, a controlled oral provocation challenge with aspirin may be performed. When patients with a history suggestive of AERD (ie, asthma, rhinosinusitis, and history of respiratory reaction to aspirin or aspirin-like drug) are challenged with aspirin, approximately 85% will have a respiratory reaction confirming the diagnosis.<sup>140</sup> A recent study showed that 100% of patients with a history of aspirin causing a severe reaction (poor response to albuterol with need for medical intervention) had positive oral aspirin challenges.<sup>141</sup>

Management of patients with AERD involves avoidance of aspirin and NSAIDs and aggressive medical and/or surgical treatment of underlying asthma and rhinitis or sinusitis. A pharmacologic induction of drug tolerance procedure (also known as aspirin desensitization), during which tolerance to aspirin can be induced and maintained, is an important therapeutic option for patients with AERD. This procedure entails administration of incremental oral doses of aspirin throughout several days, until a dosage of 650 mg (2 tablets) of aspirin can be taken without adverse reaction. Induction of drug tolerance of patients with AERD may be appropriate if aspirin or NSAIDs is therapeutically necessary or if their respiratory disease is poorly controlled with medical and/or surgical management. Aspirin desensitization treatment improves clinical outcomes for both upper and lower respiratory tract disease.<sup>247,360,361</sup> During long-term aspirin desensitization, urinary leukotriene E<sub>4</sub> decreases to baseline levels, bronchial responsiveness to leukotriene E<sub>4</sub> is greatly reduced, serum histamine and tryptase levels decrease, leukotriene C<sub>4</sub> and histamine in nasal secretions disappears, and there is a decrease in the number of respiratory cells expressing the cysteinyl leukotriene 1 receptor.<sup>133,134,610,612,613</sup>

A second clinical presentation of aspirin and NSAID drug allergic reactions is an exacerbation of urticaria or angioedema in patients with chronic idiopathic urticaria. Approximately 20% to 40% of patients with chronic idiopathic urticaria develop a worsening of their condition after exposure to aspirin or NSAIDs.<sup>614,615</sup> The rate appears to be more frequent in patients in an active phase of their urticaria or angioedema syndrome. Most patients with a history of exacerbations induced by aspirin or NSAIDs demonstrated the presence of histamine-releasing factors assessed by autologous serum skin tests and basophil histamine release assays.<sup>309</sup> All drugs that inhibit COX-1 cross-react to cause this reaction, and the arachidonic acid metabolism dysfunction

described herein is thought to play a pathogenic role. Selective COX-2 inhibitors are generally well tolerated in patients with chronic idiopathic urticaria, although there may be rare exceptions.<sup>142-144</sup>

A third type of drug allergic reaction is aspirin or single NSAID-induced urticaria or angioedema or anaphylactic reaction, in which case other NSAIDs are tolerated.<sup>145-147</sup> The underlying cause of these reactions is not fully understood. The clinical pattern of a preceding period of sensitization during which the drug is tolerated suggests an IgE-mediated mechanism, but attempts to detect drug specific IgE have been unsuccessful in most cases. However, a recent investigation of 53 patients experiencing systemic symptoms 30 minutes after ingestion of a pyrazolone (propyphenazone) revealed positive skin and enzyme-linked immunosorbent assay in vitro test results in 51 of the 53 patients.<sup>616</sup> These specific IgE tests were specific in that other pyrazolone derivatives (antipyrine, aminophenazone, or metamizol) were unable to inhibit IgE binding in the in vitro system. The reaction is not due to arachidonic acid dysfunction, and any NSAID, including selective COX-2 inhibitors, may be responsible.<sup>617,618</sup> Patients with a history of acute urticaria to aspirin are at increased risk for the subsequent development of chronic urticaria.<sup>619</sup>

A fourth type of drug allergic reaction of aspirin or NSAID allergy is urticaria or angioedema due to aspirin and any NSAID that inhibits COX-1 and thus differs from the aforementioned type of reaction in that it is nonselective. This type of reactions also occurs in individuals without a prior history of chronic urticaria.<sup>364,620</sup> These patients are usually able to tolerate COX-2 inhibitors, and their reactions are purely cutaneous without accompanying anaphylactic symptoms.<sup>142-144</sup> Patients with a history of acute urticaria to multiple NSAIDs are also at increased risk for the development of chronic urticaria.<sup>619</sup>

Rarely, patients exhibit combined (“blended”) respiratory and cutaneous reaction to aspirin or NSAIDs and hence cannot be classified into 1 of the 4 reaction types described herein. In addition, drug allergic reactions to aspirin or NSAIDs can rarely manifest as pneumonitis or meningitis. These reactions appear to be drug specific, and avoidance of all NSAIDs is not necessary.<sup>621</sup>

Allergic rashes are common adverse effects of clopidogrel, a thiopyridine inhibitor of platelet activation that is often recommended in aspirin-intolerant patients.<sup>622-624</sup> Although the mechanisms of such reactions are unknown, successful oral induction of drug tolerance protocols have been reported.<sup>622,624</sup>

Quinine-induced angioedema may occur in aspirin-intolerant patients.<sup>625</sup>

## **S. Angiotensin-Converting Enzyme (ACE) Inhibitors**

*Summary Statement 161:* ACE inhibitors are associated with 2 major adverse effects—cough and angioedema. (C)

*Summary Statement 162:* ACE inhibitor-related cough often begins within the first few weeks of treatment and occurs

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in up to 20% of patients, particularly women, blacks, and Asians. (C)

*Summary Statement 163:* The mechanism of ACE inhibitor–related cough is unclear. The cough resolves with discontinuation of the drug therapy in days to weeks. (D)

*Summary Statement 164:* Patients with ACE inhibitor–related cough are able to tolerate angiotensin II receptor blockers (ARBs). (A)

*Summary Statement 165:* ACE inhibitor–induced angioedema occurs in approximately 0.1% to 0.7% of patients and is most common in blacks. (C)

*Summary Statement 166:* ACE inhibitor–induced angioedema frequently involves the face and oropharynx and can be life-threatening or fatal. (C)

*Summary Statement 167:* The mechanism of ACE inhibitor–induced angioedema may be related to interference with bradykinin degradation. It may take months or years after initiation of therapy for a reaction to appear and often occurs sporadically despite persistent treatment. (C)

*Summary Statement 168:* ACE inhibitor–induced angioedema is treated with discontinuation of the drug therapy and subsequent avoidance of all ACE inhibitors. (D)

*Summary Statement 169:* Most patients who experience angioedema during ACE inhibitor treatment are able to tolerate ARBs. (C)

*Summary Statement 170:* Patients with a history of angioedema or C1 esterase inhibitor deficiency are at increased risk of more frequent and severe episodes of angioedema with the administration of ACE inhibitors, so they should not receive these drugs. (C)

ACE inhibitors have 2 major adverse effects—cough and angioedema. Cough occurs in up to 20% of patients, is typically dry and nonproductive, and occurs more commonly in women, blacks, and Asians.<sup>149</sup> The cough generally begins within the first few weeks of treatment, but occasionally the onset may occur much later. Aside from enzymatically converting angiotensin 1 to angiotensin 2, ACE inhibitors also normally metabolize bradykinin. ACE inhibitors allow the accumulation of bradykinin, which may cause stimulation of vagal afferent nerve fibers to produce cough. Bradykinin has also been shown to induce the production of arachidonic acid metabolites and nitric oxide, and these products may contribute to cough production through proinflammatory mechanisms.<sup>149</sup> ARBs are not associated with development of cough, the incidence of which is comparable to treatment with either placebo or diuretics.<sup>626-628</sup> There are no controlled studies on potential medical treatment of ACE inhibitor–induced cough in patients who require continued treatment.

The incidence of angioedema with ACE inhibitors is approximately 0.1% to 0.7%<sup>149,150</sup> and appears to be more common in blacks.<sup>151,152</sup> The angioedema frequently involves the face or upper airway and can be life-threatening or fatal.<sup>153,154</sup> Reports of angioedema of the intestinal tract secondary to ACE inhibitors have also been described.<sup>155</sup> Patients with C1 esterase inhibitor deficiency are at increased risk of more frequent and severe episodes of angioedema with the admin-

istration of ACE inhibitors and they should not receive these drugs. The temporal relationship between initiation of therapy with ACE inhibitors and occurrence of angioedema is unpredictable and differs from the temporal pattern of other adverse drug reactions. Patients typically take ACE inhibitors for months or even years before angioedema occurs.<sup>156</sup> It is also puzzling that recurrent episodes of angioedema occur sporadically despite continued daily use of ACE inhibitors.

ACE inhibitor–associated angioedema is often difficult to manage. Treatment includes discontinuing use of the medication and supportive care with careful management of the airway. Selected cases of refractory ACE inhibitor–induced angioedema have been successfully treated with infusion of fresh frozen plasma.<sup>629</sup> Most patients with angioedema related to ACE inhibitor usually tolerate ARBs. There are, however, case reports of occasional patients who continue to experience angioedema after being switched from ACE inhibitors to ARBs.<sup>630,631</sup> Because there is no diagnostic test to prove whether angioedema in a given patient is truly due to use of an ACE inhibitor (rather than idiopathic), these cases may not represent true cross-reactivity between these agents.

## T. Biologic Modifiers

In the past decade, a number of biologic agents have been developed to neutralize proinflammatory cytokines, their cellular receptors, and IgE antibody.<sup>157,158</sup> Because the clinical experience with these drugs varies (ie, phase IV experiences), the spectrum of reported allergic reactions may not yet be fully known for all of them. A separate type of classification for adverse reactions to biological agents has been proposed based on the mechanism of reactions (Table 3).<sup>159</sup> High-dose reactions are related to high cytokine levels administered directly or from cytokines released (cytokine release syndrome). Hypersensitivity reactions may be either antibody or cell mediated. Immune or cytokine dysregulation may result in secondary immunodeficiency, autoimmunity, or allergic or atopic disorders. Cross-reactive reactions may occur when the biologic agent is intended for a pathologic cell type but cross-reacts with normal cells. Finally, biologics may also result in nonimmunologic adverse effects.

### 1. Cytokines

*Summary Statement 171:* Allergic drug reactions ranging from cutaneous lesions to severe anaphylaxis may occur during treatment with recombinant interferons. (C)

Both  $\alpha$ - and  $\beta$ -interferons have been associated with a variety of allergic drug events. Cutaneous lesions include urticaria, atopic dermatitis, eczematous reactions at injection sites, leukocytoclastic vasculitis, and fixed drug eruption.<sup>632-637</sup> Visceral adverse events include pulmonary vasculitis and autoimmune hepatitis.<sup>638,639</sup> Life-threatening events, such as angioedema and anaphylaxis, have been reported.<sup>640,641</sup>

Allergic mechanisms may or may not play a role in thrombotic thrombocytopenic purpura or hemolytic uremic syndrome and systemic capillary permeability syndrome associ-

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ated with the use of interleukin 2 and granulocyte colony-stimulating factor, respectively.<sup>642,643</sup>

## 2. Anti-TNF- $\alpha$ Drugs

*Summary Statement 172:* Both cutaneous and systemic allergic reactions have been reported after treatment with infliximab, a human monoclonal antibody against tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). (C)

A variety of immune-mediated reactions have occurred during infliximab (Remicade) treatment for adult and juvenile rheumatoid arthritis, Crohn's disease, and psoriasis. These include urticaria, flare-up of atopic dermatitis, maculopapular rashes, leukocytoclastic vasculitis, serum sickness, and at least 7 instances of life-threatening anaphylactic reactions.<sup>160-173</sup> Severe adverse reactions, including anaphylaxis and progressive multifocal leukoencephalopathy, appear to be common in young (<10 years of age) children.<sup>644</sup> A recent retrospective evaluation of safety with this agent revealed that immediate hypersensitivity reactions (9/84 or 11%) were a major reason for discontinuation of the drug therapy.<sup>645</sup> A subset of patients experienced allergic reactions as a result of antibodies to infliximab.<sup>175</sup> Other possible immunologically related reactions include the Guillain-Barré syndrome, peripheral neuropathy, and demyelinating syndromes.<sup>646,647</sup> Fewer adverse effects have been associated with adalimumab (Humira), another recently available fully humanized TNF- $\alpha$  monoclonal antibody. These include injection site pruritic rashes and new-onset asthma.<sup>174,175</sup> New-onset asthma may also appear during treatment with both infliximab and etanercept (Enbrel). Immune-mediated reactions have also been rarely associated with the latter agent, a recombinant TNF- $\alpha$  extracellular protein domain fused to human IgG1 Fc, which neutralizes soluble TNF- $\alpha$ . These include urticaria, rashes, injection site reactions, leukocytoclastic vasculitis, lupus erythematosus, and 1 instance of lung granulomatosis injury.<sup>176-182</sup>

## 3. Monoclonal Antibodies

*Summary Statement 173:* Both cutaneous and systemic allergic reactions have been reported after treatment with both murine and humanized monoclonal antibodies. (C)

Documented episodes of anaphylaxis after administration of a chimeric anti-interleukin 2 receptor antagonist monoclonal antibody (basiliximab) and muromonab (murine anti-CD3 monoclonal antibody of the IgG2a class [OKT3]) have occurred.<sup>545,648</sup> A patient who had experienced anaphylaxis to basiliximab subsequently tolerated a humanized version (daclizumab) with impunity.<sup>649</sup> It is not yet evident whether severe allergic reactions will occur after use of visilizumab, a fully humanized anti-CD3 monoclonal antibody now in phase 1 studies.<sup>650</sup> Hypersensitivity reactions to cetuximab (chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor), including IgE-mediated anaphylaxis, has been reported to occur at a national rate of 3% or less but much higher (22%) in the Mid South region of the United States.<sup>183</sup> IgE antibodies in this condition are specific for an oligosaccharide galactose- $\alpha$ -1,3-galactose, which is present on the Fab portion of the cetux-

imab heavy chain. In most of these patients, specific IgE cetuximab antibodies were present in patients' sera before therapy.<sup>184</sup> A fatal hypersensitivity reaction after infusion of gemtuzumab oxogamicin followed by irradiated platelets was recently reported.<sup>651</sup> There have been several recent reports of immune-mediated hemolytic anemia after injections of anti-CD11a (the  $\alpha$  subunit of leukocyte function-associated antigen 1) monoclonal antibody (efalizumab).<sup>652</sup> Such reactions should be clearly distinguished from cytokine release or acute respiratory distress syndromes caused by other monoclonal antibodies (eg, rituximab).<sup>186</sup> However, severe serum sickness-like reactions have been reported after infusions of rituximab and natalizumab.<sup>653,654</sup> In 2006, 3 patients treated with natalizumab developed progressive multifocal leukoencephalopathy, resulting in 2 deaths.<sup>655</sup>

Depending on the monoclonal antibody and type of reaction, readministration strategies may include medication pretreatment, slowing infusion rates, or induction of drug tolerance.<sup>184</sup> In patients with immediate-type reactions, successful induction of tolerance to rituximab, infliximab, and trastuzumab has been reported using a 6-hour protocol in combination with corticosteroid and antihistamine premedication.

## 4. Omalizumab

*Summary Statement 174:* Rare anaphylactic reactions to anti-IgE humanized monoclonal antibody (omalizumab) were described during phase 3 clinical trials and during the post-marketing surveillance period. (C)

A combined review of spontaneous postmarketing adverse events from the US Food and Drug Administration Adverse Event Reporting System, records of the manufacturers of omalizumab, and published cases through December 2006 revealed 124 cases of anaphylaxis associated with this drug.<sup>656</sup> Many cases experienced either delayed onset (>2 hours) or protracted progression of signs and symptoms after dose administration. A contemporaneous review of omalizumab (Xolair; Genentech) clinical trials and postmarketing surveillance data by a joint task force of the major US allergy societies between June 1, 2003, and December 31, 2005, revealed 41 episodes of anaphylaxis in 35 patients. Because 39,510 patients in this database received omalizumab during the same period, this corresponded to a reporting rate of 0.103% of anaphylactic episodes.<sup>187</sup> It is noteworthy that 83 additional anaphylactic instances were reported in the 1-year interval between these 2 surveys. The Omalizumab Joint Task Force report recommended that patients receiving omalizumab should be directly observed, in a physician's office, after receiving omalizumab for 2 hours following the first 3 doses and 30 minutes after subsequent doses.<sup>187</sup>

## 5. Anticancer Monoclonal Antibodies

*Summary Statement 175:* The cytokine release syndrome must be distinguished between anaphylactoid and anaphylactic reactions due to anticancer monoclonal antibodies. (C)

The development of monoclonal antibodies for the treatment of malignant neoplasms has increased rapidly in the past decade.<sup>657,658</sup> These include rituximab (anti-CD20), trastu-

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zumab (anti-HER-2), and alemtuzumab (anti-CLL) among others. Severe symptoms, such as fever, rigors, chills, and the acute respiratory distress syndrome, may occur during administration of the first dose of the drug due to a cytokine release syndrome.<sup>185,186</sup> An extreme example of a life-threatening cytokine storm occurred in 6 healthy volunteers after receiving a superagonistic anti-CD28 monoclonal antibody.<sup>659</sup> Immune-mediated reactions, including anaphylaxis and thrombocytopenia, have also been reported.<sup>660-662</sup> Successful induction of drug tolerance to HER-2 monoclonal antibody has been documented.<sup>663</sup> The cytokine release syndrome also occurred after dosing with antisense oligonucleotides in patients with advanced leukemia.<sup>664</sup>

#### U. Complementary Medicines

*Summary Statement 176:* Allergic reactions may occur after use of complementary medicines such as bee pollen, echinacea, and vitamins. (C)

The term *complementary medicine* includes herbal products, vitamins, minerals, amino acids, and essential oils.<sup>188</sup> There is widespread belief that these products are safe because they are “natural.”<sup>189</sup> However, well-recognized adverse effects, including anaphylaxis, have been reported in patients using bee pollen products.<sup>190</sup> Allergic reactions, including asthma and anaphylaxis, have been reported after ingestion of echinacea, an herb that is derived from several species of a flowering plant.<sup>191</sup> A variety of cutaneous reactions and 1 instance of TEN have been reported after use of Chinese herbal medications, which sometimes have been adulterated with synthetic medications.<sup>192,193</sup> Herbal products, homeopathic remedies, and multivitamin-mineral complexes may be a potential risk for systemic contact dermatitis in nickel and mercury allergic patients.<sup>665,666</sup> Because the extent of this problem is unknown, patients should be questioned about the use of herbs and health supplements. Anaphylactic reactions to vitamins (particularly B<sub>1</sub> and B<sub>2</sub>) are extremely rare.<sup>667</sup> The incidence of anaphylaxis to intravenous phytonadione (vitamin K<sub>1</sub>) solubilized in Cremophor-EL was 3 per 10,000 doses.<sup>668</sup>

#### V. Other Agents

*Summary Statement 177:* *N*-acetylcysteine may cause anaphylactoid reactions. (C)

*Summary Statement 178:* Anaphylactoid reactions and deaths have been associated with intravenous iron preparations, particularly iron-dextran. (C)

*Summary Statement 179:* Life-threatening anaphylactic reactions have occurred after intravenous use of isosulfan blue and Patent Blue V dyes. (C)

*Summary Statement 180:* Anaphylactoid reactions may occur after treatment with colloid volume expanders, mannitol, Cremophor-EL, and preservatives. (C)

*Summary Statement 181:* Preservatives and additives in medications rarely cause immunologic drug reactions. (C)

*N*-acetylcysteine is the treatment of choice for paracetamol overdose. In a prospective case controlled study, 31/64

patients (48%) who received this treatment experienced anaphylactoid reactions.<sup>669</sup> Most of these reactions occurred within the first 15 minutes. Anaphylactoid reactions and deaths have been associated with intravenous iron preparations.<sup>670</sup> According to a US Food and Drug Administration surveillance database, all-event and all-fatal reporting events were highest, intermediate, and very low after administration of iron-dextran, sodium ferric gluconate, and iron sucrose preparations, respectively.<sup>670</sup>

In recent years, life-threatening anaphylactic reactions have occurred after intravenous use of isosulfan blue and Patent Blue V dyes, an adjunctive diagnostic lymphangiographic agent.<sup>671-673</sup> The results of epicutaneous skin testing and, if required, intradermal skin testing are positive in most patients.<sup>673</sup> Methylene blue dye differs structurally from both isosulfan blue and Patent Blue V, and anaphylactic reactions are rare. A recent case report of 3 melanoma patients with systemic reactions to Patent Blue V dye demonstrated epicutaneous skin test cross-reactivity to methylene blue dye.<sup>671</sup> However, confirmatory challenges were never performed, and therefore a determination of the positive and negative predictive values of such testing requires further evaluation.

Anaphylactoid reactions have been described after administration of colloid volume expanders (dextran, gelatin, hydroxyethyl starch, and human serum albumin).<sup>578</sup> An effective graded challenge protocol may be used to prevent severe anaphylactoid reactions to dextran contained in iron-dextran complexes.<sup>674</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 parenteral administration of Cremophor-EL, a solvent for paclitaxel, teniposide cyclosporine, and some anesthetics. There are also anecdotal reports of reactions to sodium benzoate and chlorobutanol, which are used as preservatives in various biologicals.

Some preservatives may evoke cough and bronchoconstriction in susceptible asthmatic patients after exposure to nebulizer solutions or formulations containing benzalkonium chloride or sulfites.<sup>206</sup> It has been suggested that susceptibility to sulfites in some asthmatic patients may be due to a deficiency of sulfite oxidase; however, most cases are due to generation of sulfur dioxide in the oropharynx.<sup>675</sup> Anecdotal instances of anaphylaxis or severe asthma have been reported in milk or soy allergic patients after inhalation of specific dry powder formulated metered dose inhalers.<sup>676,677</sup> A large randomized controlled study revealed that paradoxical bronchoconstriction occurred more often after inhalation of metered dose inhalers containing soy-derived lecithin and oleic acid than one with salmeterol alone.<sup>677</sup> In a case report, it was demonstrated that anaphylactic reactions may occur due to use of a lactose-containing dry powder inhaler in a milk allergic patient.<sup>676</sup> In vitro and in vivo testing demonstrated presence of milk protein in the dry powder device used by the patient.<sup>676</sup> This illustrates that food allergens may be hidden excipients in commonly used drug formulations.

Mannitol is occasionally used as a hyperosmolar intravenous infusion. Reactions occurring after this use are attributed to an anaphylactoid or direct mast cell mechanism. However, it is more widely used as an excipient in pharmaceutical preparations. A case report documented IgE-mediated anaphylaxis occurring after ingestion of a cisapride chewable tablet containing mannitol.<sup>678</sup>

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