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8. Drug allergy

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Drug reactions can be considered as being either predictable or unpredictable. A predictable reaction would be the result of the pharmacologic action of the medication. An unpredictable reaction might be idiosyncratic, might be drug intolerance, or might have or imply an immunologic basis, such as being IgE mediated. Immediate reactions that are not IgE mediated can be considered as pseudoallergic (non-IgE-mediated mast cell activation). This review will discuss allergic and immunologic reactions to immunomodulators, penicillins and cephalosporins, sulfonamides, aspirin, and nonselective nonsteroidal anti-inflammatory drugs and consider the serious drug-related conditions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The field of drug "allergy" has expanded to include adverse reactions associated with immunosuppressive medications, anticytokine therapies, and mAbs. The cytokine release reaction that occurs with anti-CD20 antibody infusions in patients with leukemia and white

blood cell counts of greater than $50 \times 10^9/L$ is associated with high concentrations of TNF, IL-6, and IL-8. Because of the findings of fever, dyspnea, rigors, and hypotension, this reaction resembles the Jarisch-Herxheimer reaction that occurs 60 to 90 minutes after penicillin administration in patients with secondary syphilis. Furthermore, the care of the patient with penicillin allergy has been made more difficult in the absence of the major determinant, penicilloyl-polylysine, in that from 34% to 84% of patients who have positive skin test reactions to penicillin have exclusively positive reactions to the major determinant. SJS and TEN typically are caused by medications within 1 to 8 weeks of initiation of therapy. Evidence for death of the keratinocytes through (1) drug-specific cytotoxicity with the perforin-granzyme B-mediated killing and (2) activation of Fas on keratinocytes have provided explanations for the sloughing of skin. Unfortunately, intravenous immunoglobulin therapy for SJS and TEN has been disappointing. (*J Allergy Clin Immunol* 2006;117:S464-70.)

Key words: Drug, allergy, immunosuppressive, keratinocytes, Stevens-Johnson syndrome, toxic epidermal necrolysis, penicillin

DRUG REACTIONS: GENERAL ASPECTS

One approach to assessing adverse drug reactions is to categorize them as either predictable or unpredictable.^{1,2} Predictable adverse drug reactions include (1)

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Abbreviations used

DRESS: Drug rash with eosinophilia and systemic symptoms
dsDNA: Double-stranded DNA
Fas L: Fas ligand
IVIG: Intravenous immunoglobulin
NSAID: Nonsteroidal anti-inflammatory drug
SJS: Stevens-Johnson syndrome
SLE: Systemic lupus erythematosus
TEN: Toxic epidermal necrolysis

toxicity from medication, (2) unavoidable side effects, (3) pharmacologic actions, and (4) drug-drug interactions.^{1,2} Unpredictable adverse drug reactions include (1) intolerance, in which the patient experiences expected reactions at much lower doses or blood concentrations than usual; (2) idiosyncratic reactions, which often are attributable to genetic or pharmacokinetic responses that cause reactions not occurring in other subjects; and (3) allergic (IgE-mediated) or pseudoallergic (non-IgE-mediated) reactions.

The designation of allergic drug reactions falls under the category of adverse drug reactions, which itself falls under the umbrella of adverse drug events. The medical literature has been expanded to consideration of adverse drug reactions and their causes (systematic inefficiencies or physician, nurse, or pharmacist errors) in the context of improving the system-wide delivery of health care.³⁻⁹ The term *adverse drug events* encompasses a more broad approach of which adverse drug reactions are one part. Adverse drug events are defined as medication-induced injuries and have been estimated to result in from 3% to 9% of hospital admissions⁸ and to occur in as many as 81% of inpatients.¹⁰ Adverse drug events were reported to occur in 25% of outpatients who had received at least 1 prescription and were monitored closely over a 3-month period.⁷ With the current emphasis on reducing medication errors, in the analysis of adverse drug events, often there is more than a single point of error or absence or failure of a safety net process. Such findings of missed opportunities are analogous to investigations of errors in other industries, such as air travel.^{3,4,9}

IMMUNOMODULATORS

Immunosuppressant medications, cytokines and anti-cytokines, and mAb therapies have become commonplace for treatment of neoplastic diseases, Crohn's disease, and rheumatoid arthritis. Omalizumab is being used for patients with persistent asthma. Several medications have been reported to produce anaphylactic or other serious allergic-type or toxic reactions. Cyclosporine, which is used for immunosuppression in patients undergoing transplantation, suppresses T-cell activation and inhibits IL-2 by blocking the effects of the phosphatase calcineurin. Cyclosporine can be administered to patients with

refractory idiopathic urticaria, but side effects can include an acute hypertensive reaction, reductions in the glomerular filtration rate, and hypertrichosis. Anaphylactic reactions have been reported after intravenous^{11,12} administration, and some patients have immediate (within 20 minutes) cutaneous reactivity to cyclosporine. The same patients have tolerated oral cyclosporine. It was proposed that the immediate reactions are attributable to the stabilizer, cremophor el (BASF Aktiengesellschaft, Ludwigshafen, Germany), which is hydrogenated castor oil and is present in the intravenous preparation but not in oral capsules (that have corn oil, some with gelatin).^{11,12} A patient might have been treated with oral cyclosporine uneventfully for graft-versus-host disease but experience 5 diarrhea stools a day. The cyclosporine then is administered intravenously, and anaphylactic shock and respiratory failure occur.¹¹ On the basis of case reports, the same patient can resume oral cyclosporine without anaphylaxis occurring.¹² Some caution is necessary because a very rare patient has experienced anaphylactic shock from oral cyclosporine, and skin testing with cyclosporine has not been validated.¹³ Some examples of other allergic-like or immunologic effects from immunomodulatory therapies are presented in Table I.¹¹⁻²¹

The therapeutic administration of anticytokine preparations can cause acute urticaria or anaphylaxis or other adverse immunologic effects. Indeed, there is great concern about the use of anti-TNF- α therapy and the development of anti-DNA and anti-nuclear antibodies.¹⁶ Infliximab, a chimeric (murine and human) IgG₁ κ antibody, binds to soluble and membrane-bound TNF- α . It has been used for the treatment of patients with rheumatoid arthritis and has been associated with production of anti-double-stranded DNA (anti-dsDNA) antibodies in 10% to 14% patients, as well as clinical but reversible systemic lupus erythematosus (SLE).¹⁷ As with infliximab, etanercept, a soluble inhibitor of TNF- α , has been associated with this phenomenon and development of reversible SLE.¹⁶ It has been proposed that the anti-TNF- α antibody that binds to TNF- α on cells induces cell death with release of nucleosomal autoantigens that would result in production of anti-DNA antibodies.¹⁶ When administered to patients with rheumatoid arthritis, these agents are coadministered with methotrexate in the hope of not inducing clinical SLE.¹⁸ IFN- α , used for the treatment of hepatitis B and C, lymphoma, leukemia, and carcinoid tumors, infrequently causes urticaria or angioedema but is known to result in production of antithyroid antibodies and either hypothyroidism or hyperthyroidism.¹⁶ Autoimmune thyroiditis has been described after treatment with IL-2, which is used for its antitumor effects for carcinoma, malignant melanoma, and other conditions.¹⁶

After administration of anti-tumor cell antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52), and with an anti-CD3 antibody used in new-onset diabetes mellitus, there is acute onset of temperature increase, rigors, dyspnea, and hypotension.^{20,21} Currently referred to as the *cytokine release reaction*, there is clinical similarity to the Jarisch-Herxheimer reaction, which occurs from

TABLE I. Selected examples of allergic-like or immunologic effects of immunomodulatory therapies

Agent	Effects
Cyclosporine	Anaphylaxis or pseudoallergic reactions (possibly from the stabilizer, cremophor el, in the intravenous preparation)
Mycophenolate	Anaphylaxis or pseudoallergic reactions (possibly from 25 mg of polysorbate 80 in the intravenous preparation)
Sirolimus	Angioedema
Thalidomide	Maculopapular rashes, SJS, TEN
Infliximab, etanercept	Anti-dsDNA antibodies, reversible SLE
IFN- α	Urticaria, angioedema, anti-thyroid antibodies
IL-2	Autoimmune thyroiditis
Rituximab, alemtuzumab	Rigors, dyspnea, hypotension, urticaria

Data are from references 11-21.

60 to 90 minutes after parenteral penicillin is administered to patients with syphilis. It is recognized that there is an increase of circulating concentrations of TNF- α , IL-6, and IL-8.^{20,21} The Jarisch-Herxheimer and cytokine release reactions remain in the differential diagnosis for anaphylaxis. There are reports of anaphylactic reactions, urticarial reactions (on day 7), and serum sickness to mAbs. For example, urticaria occurred on day 7 in 7 of 12 patients receiving a humanized antibody to CD3 for treatment of type 1 diabetes mellitus.²¹ Serum sickness can be expected with administration of antithymocyte globulin (equine or rabbit in origin) for treatment of pure red cell aplasia or for transplantation immunosuppression.²² Despite the coadministration of corticosteroids and either azathioprine or mycophenolate mofetil, 18 of 240 patients had serum sickness from days 10 to 14 when receiving a rabbit-generated antithymocyte globulin.²²

In summary, immunomodulatory therapy has been associated with adverse effects, including production of dsDNA and anti-nuclear antibodies and apparently reversible SLE. The expected less common anaphylactic or delayed urticarial rash and serum sickness reaction can occur even when the biologic modifier or recombinant mAb has identical primary (amino acid) structure as the human equivalent. These observations suggest that the conformational (tertiary) structure might be different from that of native molecules as a consequence of the manufacturing process. What has been happening in recent years with the array of new biologic modulators is consistent with the previous demonstration of allergic reactions to recombinant insulin, in which some patients were found to be even more reactive to recombinant insulin than porcine insulin!²³

PENICILLINS AND CEPHALOSPORINS

After administration, penicillin is degraded (in the absence of an enzymatic process) to major determinants (95% of transformation) and minor determinants (5%

of transformation). These determinants serve as immunogenic haptens for binding to albumin or IgG. The use of reagents known as major and minor determinants has allowed allergists-immunologists to demonstrate anti-penicillin (determinant) IgE antibodies to identify which patients have anti-penicillin IgE and which patients do not. However, as of October 2004, the major determinant, penicilloyl-polylysine (Pre-Pen; Holister Stier, Spokane, Wash), has not been available commercially. If patients are skin tested with several minor determinants of penicillin but not penicilloyl-polylysine, from 34% to 84% of patients with positive skin test responses will be missed.²⁴⁻²⁶ Fortunately, about 82% of patients who report a history of penicillin allergy will be found to have negative skin test responses by using major and minor penicillin determinants, but a large percentage of the positive with true-positive responses would not be identified without the use of penicilloyl-polylysine.^{25,26} Furthermore, approximately 33% of patients with positive penicillin skin test responses have a vague history of a reaction.²⁷ In other words, the absence of penicilloyl-polylysine interferes with the accurate assessment of patients with penicillin allergy as far as their current presence of anti-penicillin IgE antibodies.

Why is the absence of penicilloyl-polylysine so important? First, if the major and 3 minor determinants of penicillin are nonreactive, there is a negative predictive value of 99% during subsequent penicillin or β -lactam drug administration.²⁶ A test dose of 3 to 5 mg can be given first, followed by the therapeutic dose.

Second, the theoretic risk of a course of penicillin resensitizing the patient with a positive history but a negative skin test response has been shown to be low and is on the order of 3% or less.^{28,29} Thus once a patient with a positive history is shown to have a negative skin test response and tolerates a course of penicillin or β -lactam drug, future administration of such agents would not require additional skin testing or test-challenges.

Third, if the patient with penicillin allergy just is skin tested to minor determinants and found to have negative responses, then the negative predictive value for no anaphylactic reaction to penicillin or β -lactams is considerably less. Test dosing (a supervised challenge) is required, such as with oral doses of 3 mg, 30 mg, and 220 mg for a target of 250 mg of penicillin or amoxicillin. It is hoped that the exquisitely reactive patient will react to 30 mg with generalized erythema or limited urticaria so that the challenge can be stopped.

Test doses should not be carried out when there is a history of penicillin-induced blistering or skin sloughing, mucocutaneous eruptions, hepatitis, interstitial nephritis, or hemolytic anemia. There should be a clear indication for the penicillin medication with approval by the patient or responsible party. The allergist-immunologist often is asked to consider the readministration of an incriminated mediation or therapeutic agent. In some cases the patient was labeled "allergic to penicillin," although vancomycin also was being administered when a generalized rash occurred.

When a patient with penicillin allergy requires a cephalosporin, the risk of a cephalosporin reaction is much lower going from the first generation (5% to 16.5%) to the second generation (cefazolin 4%) and the third or fourth generation (1% to 3%).¹ There remains some controversy over whether these reactions are cross-reactivity or independent reactions in a susceptible population. The patient with penicillin allergy does experience more cephalosporin-induced allergic reactions (up to an 8-fold increase) than do patients without penicillin allergy.³⁰ Patients with penicillin allergy with negative skin test responses to major and minor penicillin determinants can tolerate a cephalosporin without an allergic reaction.^{30,31} The positive predictive value of cephalosporin skin tests has not been documented, but data suggest a high negative predictive value using parent cephalosporins at 2 mg/mL.³² Challenges were begun with 0.01 followed by 0.1 and full doses of the cephalosporin administered hourly in patients with negative cephalosporin skin test responses.³² No allergic reactions occurred in the 101 patients challenged.³²

SULFONAMIDES

Sulfonamide-induced allergic reactions occur in as many as 29% to 65% of patients with HIV-AIDS compared with in 2% to 4% of other patients.^{1,33} Often patients with HIV-AIDS have morbilliform (maculopapular), nonpruritic, nonblistering rashes, as can patients without HIV-AIDS. Acute urticarial reactions to sulfamethoxazole or trimethoprim are infrequent. Nonurticarial rashes and hypersensitivity (Stevens-Johnson syndrome [SJS]) to sulfonamides are thought to be attributable to reactive metabolites (oxidative products termed hydroxylamines) that cannot be reduced fully by glutathione stores.³³ Using caffeine as a marker for the N-acetylation of sulfonamides, slow acetylation has been reported to exist in affected patients, which would favor metabolism of the sulfonamide into reactive toxic metabolites.³⁴ Oxidation of sulfonamides into nitroso metabolites also can participate in sulfonamide-induced allergic reactions.

There has been unsubstantiated information that a person who is allergic to a sulfonamide would be allergic to nonantibiotic sulfonamides. Retrospective data from a large database of general practitioners in the United Kingdom in part help refute this notion.³⁵ Patients with a presumed allergic reaction within 30 days of receiving a sulfonamide antibiotic (sulfamethoxazole-trimethoprim in 98.4% of cases) were compared with patients who similarly received the sulfonamide antibiotic but did not react.³⁵ It should be mentioned that an allergic reaction included "asthma, eczema, and unspecified adverse effects of a drug."³⁵ Such allergic reactions, occurring within 30 days of administration of a sulfonamide nonantibiotic, were reported in 9.9% of patients with a prior hypersensitivity reaction to a sulfonamide antibiotic compared with 1.6% of patients without a prior reaction to a sulfonamide antibiotic.³⁵ Thus approximately 90% of patients

labeled as having sulfonamide allergy did not have a reaction to a sulfonamide nonantibiotic. Unexpectedly, an allergic reaction to a penicillin was found to occur in 14% of patients with a prior hypersensitivity reaction to a sulfonamide antibiotic compared with 2% of patients without such hypersensitivity. Because there were more reactions to penicillins than to sulfonamide nonantibiotics (14.0% vs 9.9%), the data raised the possibility that patients who have reacted to sulfonamide antibiotics have increased susceptibility to experience allergic-type reactions to other medications. Alternatively, the findings point out that patients might be labeled allergic to medications when either the physician, health care provider, or patient falsely attributes acute symptoms of asthma or eczema or other symptoms to the recently prescribed medication. With the same data set and restricting the definition to an allergic reaction to include urticaria, anaphylactic shock, erythema multiforme, and drug allergy, only 86 (0.4%) of 20,279 patients had an allergic reaction within 30 days of the sulfonamide antibiotic.³⁵ Just 19 (0.1%) of 20,391 patients reported an allergic reaction to the subsequent nonantibiotic sulfonamide.³⁵ These data support the notion that although patients labeled allergic to sulfonamides might be at increased risk of untoward reactions to penicillins, they do not appear to be as likely to experience allergic reactions to sulfonamide nonantibiotics.

ASPIRIN AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are relatively contraindicated in patients with chronic idiopathic urticaria because from 21% to 30% of patients will have urticaria or angioedema on rechallenge.^{1,36-38} Alternatively, COX-2 selective medications are tolerated in almost all cases, but their long-term use is complicated by the increased risk of cardiovascular complications. It has been reported that aspirin desensitization for chronic idiopathic urticaria is not likely to be successful in contrast to the many cases of successful desensitization of aspirin-induced respiratory disease.^{37,38} If a patient has acute urticaria, angioedema, or anaphylaxis from a single nonselective NSAID and is not a patient with aspirin-induced respiratory disease, it might be possible to administer either aspirin or another NSAID safely through test dosing or actual desensitization. The COX-2 inhibitors had been administered safely to such patients but are not an option at this time.

Aspirin and nonselective NSAIDs inhibit COX-1, which results in decreases in thromboxanes and prostaglandins, including prostaglandin E₂. This prostaglandin has inhibiting effects on 5-lipoxygenase-activating protein and 5-lipoxygenase, which participate in the generation of 5-hydroperoxyeicosatetraenoic acid in the leukotriene pathway.³⁷ Therefore after aspirin or nonselective NSAID administration, there is reduced production of thromboxanes and prostaglandins and increased production of leukotrienes B₄ and C₄, the latter of which is

TABLE II. Examples of high-, moderate-, and low-risk situations involving drug allergies

Higher-risk situations (estimated to be from 50% to 95%)

1. Administration of a β -lactam antibiotic to a patient within 1 year of a convincing allergic reaction to penicillin^{1,24,36}
2. Penicillin skin test reactions are positive, and the patient receives a bolus infusion of a β -lactam antibiotic⁴⁸
3. Cross-reactivity between penicillin and imipenem^{36,49}
4. Cross-reactivity between phenytoin and carbamazepine in terms of SJS or TEN^{1,50}
5. Readministration of phenobarbital to a patient who had experienced a blistering rash from phenobarbital¹
6. Cross-reactivity or acute angioedema reactions among angiotensin-converting enzyme inhibitors in susceptible patients^{1,51,52}
7. A clinical setting in which opportunities for patient safety are overlooked

Moderate-risk situations (estimated to be from 30% to 50%)

1. An aspirin-intolerant patient with asthma receiving an initial full dose of a nonselective NSAID^{1,36,53}
2. Administration of a β -lactam antibiotic to a patient with a convincing history of penicillin allergy 5 years previously²⁴

Lower-risk situations (estimated to be from 0% to 5%)

1. Patient with penicillin allergy has negative skin test reactions to major and minor penicillin determinants and receives a β -lactam or cephalosporin^{1,24,26,31,36,54}
2. Administration of a β -lactam antibiotic to a patient with a convincing history of a penicillin allergy 25 years previously (skin testing and test dosing still are indicated)
3. A patient with SJS from phenytoin or carbamazepine receives valproic acid³⁶
4. A patient with nonselective NSAID-induced asthma or urticaria receives a COX-2 antagonist⁵⁵⁻⁵⁸
5. A patient with acute angioedema from an angiotensin-converting enzyme inhibitor receives an angiotensin receptor blocker^{1,59}
6. A patient who experienced anaphylactic shock from radiographic contrast medium who is pretreated with prednisone (–13, –7, and –1 hour) and diphenhydramine (–1 hour) and receives a lower osmolality contrast medium^{1,60}
7. A patient with sulfamethoxazole-induced maculopapular rash who receives furosemide or other nonantibiotic sulfonamide

metabolized to the reactive agonist leukotriene D₄. In addition, for patients with aspirin-induced asthma, there is a substantial increase in baseline leukotriene E₄ levels, reflecting synthesis of leukotriene D₄, which increases 10-fold after aspirin administration. Starting doses (10 mg) of aspirin and protocols for testing patients with coronary artery disease have been published.³⁷

SJS, TOXIC EPIDERMAL NECROLYSIS, AND DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

SJS is a severe, diffuse mucocutaneous eruption causing erythematous or purpuric macules, blisters, target lesions, and no more than 10% skin detachment. Other manifestations are fever and mucosal lesions (stomatitis, conjunctivitis, or urethral inflammation) accompanied by at least 1 other visceral organ, such as hepatic, renal, or gastrointestinal involvement. Toxic epidermal necrolysis (TEN) involves 30% or more skin detachment. When there is from 10% to 30% skin detachment, the designation SJS-TEN overlap syndrome is used. Medications are implicated for nearly all cases of TEN, and about 75% of SJS cases can be attributed to medications, with culprits including sulfonamides, phenytoin, carbamazepine, phenobarbital, lamotrigine, penicillins, and allopurinol.^{1,39,40} SJS and TEN occur within 1 to 8 weeks after administration of incriminated medications in most cases. The shorter durations occur in sensitized patients who have had previous milder cutaneous eruptions to the medications.

There continues to be dispute about whether SJS and TEN are attributable to a similar pathogenetic mechanism. The skin biopsy specimens of patients with TEN show few lymphocytes that are of the CD8⁺ phenotype.⁴¹ Initial experimental findings from patients with either SJS or TEN suggested that the keratinocytes expressed both the death receptor CD95 (Fas) and its ligand (Fas L).^{42,43} Sera from patients were found to have at least 3-fold higher concentrations of Fas L, which was a result of cleavage of what had been membrane-bound Fas L.⁴³ These experiments suggested that intravenous immunoglobulin (IVIG) might be effective if it contained sufficient quantities of anti-Fas activity so that Fas L could not bind to Fas. These experiments led to attempts to treat TEN and SJS with IVIG; unfortunately, the results have been disappointing,⁴⁴ but the IVIG preparations were not always analyzed for anti-Fas activity. Subsequently, studies of TEN blister fluid have identified cytotoxic CD8⁺, HLA-DR, CD56⁺ lymphocytes that are able to kill autologous keratinocytes, the latter obtained from trypsinization of hair follicles from affected patients.⁴¹ The blister fluid lymphocytes stained for granzyme B, and these results are consistent with earlier findings of markedly increased expression of TNF- α , perforin, and granzyme B from blister fluid in SJS and TEN. Thus the SJS and TEN blister studies suggest that there are cytotoxic CD8⁺ lymphocytes that cause perforin-granzyme B mediated necrosis of keratinocytes.⁴¹

Drug rash with systemic symptoms and eosinophilia (DRESS) syndrome would appear to be a form of SJS but includes lymphadenopathy and hepatic involvement, along with a generalized exfoliative dermatitis, fever, eosinophilia, and leukocytosis.⁴⁵ Culprit medications are carbamazepine, phenytoin, sulfonamides, and allopurinol

as examples. Some cases are attributable to herpesvirus 6 infection. Early recognition of the systemic aspects of DRESS with cessation of suspect medications is required. Systemic corticosteroids are recommended for DRESS and SJS but not for TEN, which has sloughing of more than 30% of the skin and resembles a burn.⁴⁶ Transfer to a burn unit usually is needed for patients with TEN. It remains controversial, but corticosteroids have been helpful in resolving cases of DRESS and SJS.⁴⁶ In 67 patients with SJS treated at Northwestern University with systemic corticosteroids, all patients recovered, although 3 patients subsequently succumbed from other causes.⁴⁷ Prompt cessation of potential incriminated medications is very important as well.

SUMMARY

The use of immunomodulatory therapies has led to an appreciation of adverse reactions ranging from anaphylaxis from mAbs to anti-dsDNA antibodies and reversible SLE from infliximab and etanercept. The cytokine release reaction that occurs with administration of rituximab and atemlizumab resembles the Jarisch-Herxheimer reaction from penicillin treatment of syphilis. From a diagnostic perspective, in patients with a history of penicillin allergy, the assessment of the patient's current anti-penicillin IgE antibodies has been made more difficult by the unavailability of the penicillin major determinant. Test challenges in patients with penicillin allergy or other patients should be carried out cautiously as in the past and with the indication for testing clearly apparent. Some examples of high-, moderate-, and low-risk situations regarding various clinical presentations of drug allergies are presented in [Table II](#).^{1,24,26,31,36,48-60} Cephalosporins are tolerated by essentially all patients with penicillin allergy after negative skin testing with major and minor determinants. Anaphylaxis can occur from seemingly well-tolerated immunosuppressants or mAbs and yet be the first witnessed anaphylactic reaction presenting to the non-allergist-immunologist health care provider. Efforts to anticipate, prevent, and treat untoward reactions to new or older therapies will continue to be necessary to improve care for patients with drug allergies.

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9. Food allergy

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Food allergy, defined as an adverse immune response to food proteins, affects as many as 6% of young children and 3% to 4% of adults. Food-induced allergic reactions are responsible for a variety of symptoms involving the skin, gastrointestinal tract, and respiratory tract and might be caused by IgE-mediated and non-IgE-mediated (cellular) mechanisms. Our understanding of how food allergy represents an abrogation of normal oral tolerance is evolving. Although any food can provoke a reaction, relatively few foods are responsible for the

vast majority of significant food-induced allergic reactions: milk, egg, peanuts, tree nuts, fish, and shellfish. A systematic approach to diagnosis includes a careful history, followed by laboratory studies, elimination diets, and often food challenges to confirm a diagnosis. Many food allergens have been characterized at a molecular level, which has increased our understanding of the immunopathogenesis of food allergy and might soon lead to novel diagnostic and therapeutic approaches. Currently, management of food allergies consists