

10. Drug allergy

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Adverse drug reactions are common, but only 6% to 10% are immunologically mediated. Unlike most adverse drug reactions, allergic drug reactions are unpredictable. Whereas some drug-induced allergic reactions may be easily classified into one of the four Gell and Coombs hypersensitivity categories, many others that appear to have an immunologic component cannot be classified because of our lack of mechanistic information. Theoretically, any drug can induce an immune response. However, some drugs are more likely to elicit clinically relevant immune responses than are others. Drugs in this category include antimicrobial drugs, anticonvulsants, chemotherapeutic agents, heparin, insulin, protamine, and biologic response modifiers. After a drug-disease connection is established, it must be determined whether the reaction was immunologically mediated. Subsequently, confirmatory tests, if available, should be used to determine the allergic status of the patient. If these tests are not available, a graded challenge or desensitization may be considered, depending on the type of clinical reaction previously demonstrated and the need for drug readministration. Education of the patient and primary care physician is an important component of patient management. (*J Allergy Clin Immunol* 2003;111:S548-59.)

Key words: Adverse drug reaction, allergic drug reaction, hypersensitivity syndrome, hapten hypothesis, antimicrobial drugs, penicillins, skin testing, graded challenge, desensitization

EPIDEMIOLOGY OF DRUG-INDUCED ALLERGIC REACTIONS

Allergic drug reactions are one type of adverse drug reaction (ADR). An ADR has been defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment.¹ Although ADRs are common, it has been difficult to determine their true frequency because adequate reporting mechanisms do not exist. For similar reasons, determining the incidence and prevalence of allergic drug reactions has been challenging as well.

Although it has been difficult to determine the frequency of drug-induced allergic reactions specifically, it is known that they account for only a small proportion of ADRs. To determine the frequency of cutaneous allergic reactions to drugs introduced after 1975, Bigby et al² analyzed data on 15,438 consecutive medical inpatients who had been monitored by the Boston Collaborative Drug Surveillance Program from June 1975 to June 1982.

Abbreviations used

ADR:	Adverse drug reaction
DRESS:	Drug reaction with eosinophilia and systemic symptoms
HSS:	Hypersensitivity syndrome
NSAID:	Nonsteroidal anti-inflammatory drug
PPL:	Penicilloyl polylysine
SJS:	Stevens-Johnson syndrome
TEN:	Toxic epidermal necrolysis

Drug-induced adverse events were well characterized for each patient, and cutaneous reactions that were acceptable for further analysis consisted of only those reactions that were known or presumed to be allergic in nature.

Three hundred fifty-eight cutaneous reactions occurred in 347 patients, yielding a mean reaction rate of 2.2%. Most of the reactions (94%) were morbilliform eruptions. Five percent were urticarial. For each of the 51 drugs studied, the number of reactions per 1000 drug administrations was determined, and reaction rates were calculated. Reaction rates were as follows: amoxicillin, 5.1%; trimethoprim-sulfamethoxazole, 3.4%; ampicillin, 3.3%; blood products, 2.2%; cephalosporins, 2.1%; semisynthetic penicillins, 2.1%; erythromycin, 2.0%; and penicillin G, 1.8%. Thus, in this study, antibiotics accounted for most drug-induced cutaneous allergic reactions.

More recently, the epidemiology of drug-induced anaphylaxis has been evaluated. In 1999, Laxenaire³ published the fourth French survey of anaphylaxis during general anesthesia. Members of the Perioperative Anaphylactoid Reactions Study Group identified and evaluated patients in whom anaphylaxis had occurred during anesthesia from July 1994 to December 1996. One thousand six hundred forty-eight patients were identified and skin tested. An IgE-mediated mechanism accounted for 692 of the reactions (characteristic clinical symptoms and positive skin test results), and another 611 were judged to be anaphylactoid in nature (characteristic clinical symptoms and negative skin test results). The remaining 345 cases could not be categorized. The most common agents that provoked IgE-mediated anaphylactic reactions were muscle relaxants and latex.

Fatalities as a result of drug-induced anaphylaxis have been recorded in several studies. On the basis of information gathered by the Danish Committee on Adverse Drug Reactions and the Central Death Register, 30 cases of fatal drug-induced anaphylaxis were identified in Denmark from 1968 through 1990. The most common causes were contrast media, antibiotics, and allergenic extracts.⁴ More recently, Pumphrey⁵ searched death certificates in the United Kingdom for anaphylactic causes of death during the interval from 1992 through 1998. One hundred

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sixty-four anaphylactically induced fatalities were identified, and 39% of these were drug induced. The most common drug causes were anesthetics (27 cases), antibiotics (16 cases), and contrast media (8 cases).

CLASSIFICATION OF DRUG-INDUCED ALLERGIC REACTIONS

ADRs are grouped into two broad categories, those that are predictable, common, and related to the pharmacologic actions of the drug (type A reactions) and those that are unpredictable, uncommon, and usually not related to the pharmacologic actions of the drug (type B reactions).⁶ Approximately 80% of ADRs fall into the first category, and typical examples are drug-induced toxicity, side effects, secondary effects, and drug interactions. Immune-mediated or allergic drug reactions fall into the second category. Like other type B reactions, these reactions are uncommon, comprising only 6% to 10% of all ADRs.⁷

Unlike type A reactions, type B reactions often are not manifested until after a drug is marketed. Moreover, their development appears to be dependent on both genetic and environmental factors. Reactions in this category include drug intolerance (an undesired drug effect produced by the drug at therapeutic or subtherapeutic dosages), idiosyncratic reactions (uncharacteristic reactions that are not explicable in terms of the known pharmacologic actions of the drug), and allergic or hypersensitivity reactions (reactions that are dependent on one or more immunologic mechanisms).

Allergic reactions can be further classified according to the Coombs and Gell⁸ classification system into immediate-type hypersensitivity reactions (mediated by drug-specific IgE antibodies), cytotoxic and immune complex reactions (mediated by drug-specific IgG or IgM antibodies), and delayed-type hypersensitivity reactions (mediated by drug-specific T lymphocytes). Although these categories seem relatively straightforward, classifying most drug reactions into one or more of them can be quite a challenge because of our lack of mechanistic information regarding these reactions.

PATHOGENESIS OF DRUG-INDUCED ALLERGIC REACTIONS

Because of their macromolecular form, some drugs, such as peptide hormones, are intrinsically immunogenic. Many drugs, however, have a molecular mass of less than 1000 daltons and are incapable of inducing an immune response in their native state. For these agents to become effective immunogens, they not only must bind covalently to high-molecular weight proteins but also must undergo successful antigen processing and presentation.

Our understanding of the immune response to drug antigens is based primarily on the hapten hypothesis.⁹ Some drugs, such as penicillin, can be directly chemically reactive as a result of the instability of their molecular structure. Others, however, must be metabolized, or bioactivated, to a reactive form before an immune response can be

initiated. Although bioactivation is typically mediated by cytochrome P₄₅₀ enzymes in liver hepatocytes, it may also occur at other sites, such as skin keratinocytes.

Bioactivation is usually followed by a bioinactivating process. In some cases, however, genetic or environmental factors may perturb the balance between these two processes, leading to increased formation or decreased elimination of reactive drug metabolites. Once formed, these reactive species may do one of several things. (1) They may bind to macromolecules and cause direct cellular damage. (2) They may bind to nucleic acids to produce an altered gene product. (3) They may bind covalently to larger macromolecular targets, form an immunogenic complex, and induce an immune response.

IMMUNE REACTIONS TO ANTIMICROBIAL DRUGS

Penicillin and other β -lactam drugs

Allergy to β -lactam drugs is commonly reported, especially penicillin allergy. The most common β -lactam-induced drug reactions are maculopapular or morbilliform and urticarial eruptions. However, severe anaphylactic reactions can and do occur on rare occasions. A review of penicillin-induced anaphylaxis that was done in the late 1960s evaluated data from both published and unpublished reports and found an occurrence rate of 1.5 to 4 cases per 10,000 treated patients.¹⁰ Subsequently, a prospective international study was performed to determine the incidence of allergic reactions to monthly intramuscular benzathine penicillin injections that were administered to prevent rheumatic fever recurrences. One thousand ninety patients from 11 countries were enrolled. After 32,430 injections during 2736 patient years of observation, 57 of 1790 patients (3.2%) had an allergic reaction, and 4 of these reactions were anaphylactic (incidence of 0.2%; 1.2 cases/10,000 injections).¹¹ Despite the fact that penicillin-induced anaphylaxis is rare, this drug continues to be the most common cause of anaphylaxis in human beings, accounting for approximately 75% of fatal anaphylactic cases in the United States each year.^{12,13}

The penicillins have been the most extensively studied antibiotic family, and for this reason much is known about their immunochemistry. All penicillins contain both a β -lactam ring and a thiazolidine ring. In addition, each can be distinguished by the nature of the R side-chain group (Fig 1). Whereas most other haptenic drugs, such as the sulfonamides, must be metabolized before they react with proteins to form immunogenic complexes, penicillin is intrinsically reactive because of its β -lactam ring. Because of its instability, this ring structure readily opens, allowing the carbonyl group to form amide linkages with amino groups of lysine residues on nearby proteins.¹⁴ Because approximately 95% of penicillin molecules bind to proteins in this manner, the antigenic determinant formed, benzyl penicilloyl, has been termed the major penicillin determinant. After its identification, penicilloyl determinants were coupled to a weakly

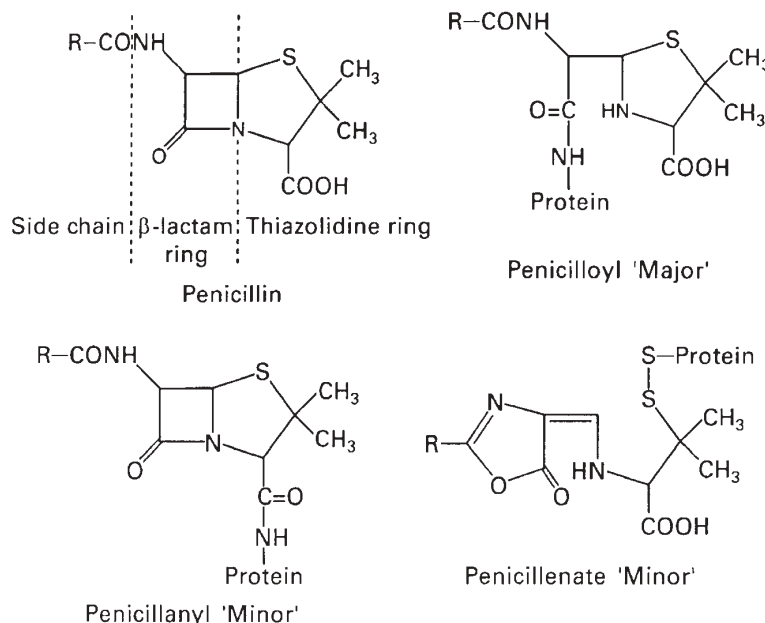


FIG 1. General structure of penicillins and structures of the major and minor penicillin antigenic-allergenic determinants, showing point of attachment of the drug to the carrier. From Baldo B. Penicillins and cephalosporins as allergens—structural aspects of recognition and cross-reactions. *Clin Exp Allergy* 1999;29:745. Used with permission.

immunogenic polylysine carrier to form penicilloyl polylysine (PPL), which is now commercially available.

In addition to the penicilloyl determinant, several other minor penicillin determinants are formed, and these too have been shown to elicit IgE-mediated responses in human beings. Because of their importance, not only should PPL be used as a testing reagent when evaluating patients for the presence of penicillin-specific IgE antibodies, but a mixture of minor determinants should also be used. The original minor determinant mixture that was developed and analyzed consisted of benzylpenicillin, its alkaline hydrolysis product (benzylpenicilloate), and its acid hydrolysis product (benzylpenilloate).¹⁵

It has been well documented that patients with a positive history but negative skin test results with PPL and minor determinant mixture rarely have IgE-mediated reactions on penicillin readministration.¹⁶⁻¹⁹ If such reactions do occur, they are mild and self-limited, and anaphylaxis has never been reported in a person with a negative penicillin skin test.²⁰

PPL (Pre-Pen) is the only commercially available penicillin skin test reagent. Unfortunately, the use of this reagent alone could cause as many as 25% of all potential positive skin test reactions to be missed.¹⁸ If fresh (not aged) benzylpenicillin G is used (at a concentration of 10,000 U/mL) as the only minor determinant (along with PPL), 5% to 10% of potential positive skin test reactions will be missed.^{18,21} Some of the missed persons may be at risk for development of anaphylaxis if penicillin is readministered.²²

In addition to the antigenic determinants that are formed from the β -lactam ring structure, the side-chain group that distinguishes the different penicillins also may elicit the production of IgE antibodies that are clinically significant. Thus, specific tests for individual penicillins may be needed, as opposed to simply using major and minor determinant preparations made from benzylpenicillin. The importance of side-chain-specific antibodies was recently demonstrated in a study by Baldo²³ in which the IgE-binding specificity was evaluated in patients who had reacted to flucloxacillin. Quantitative hapten inhibition studies demonstrated that only dicloxacillin, cloxacillin, and oxacillin (penicillins that have an R group similar to that in flucloxacillin) were able to strongly inhibit IgE binding. Penicillins that did not possess a methyl-phenyl-isoxazolyl side-chain determinant were poor inhibitors. These results indicate that, at least for some β -lactam-allergic persons, the IgE antibodies that are formed may be directed toward the R group of the β -lactam drug and not to the determinants formed by the β -lactam or the thiazolidine rings. This finding suggests that different penicillins may be cross-reactive, not only by virtue of their shared β -lactam and thiazolidine rings but also by virtue of shared or similar side-chain determinants. Because we do not have any skin test reagents for the semisynthetic penicillins in this country and thus do not have side-chain-specific reagents, it is helpful to have knowledge of the side-chain. Fig 2 lists the various semisynthetic penicillins and their structural similarities.

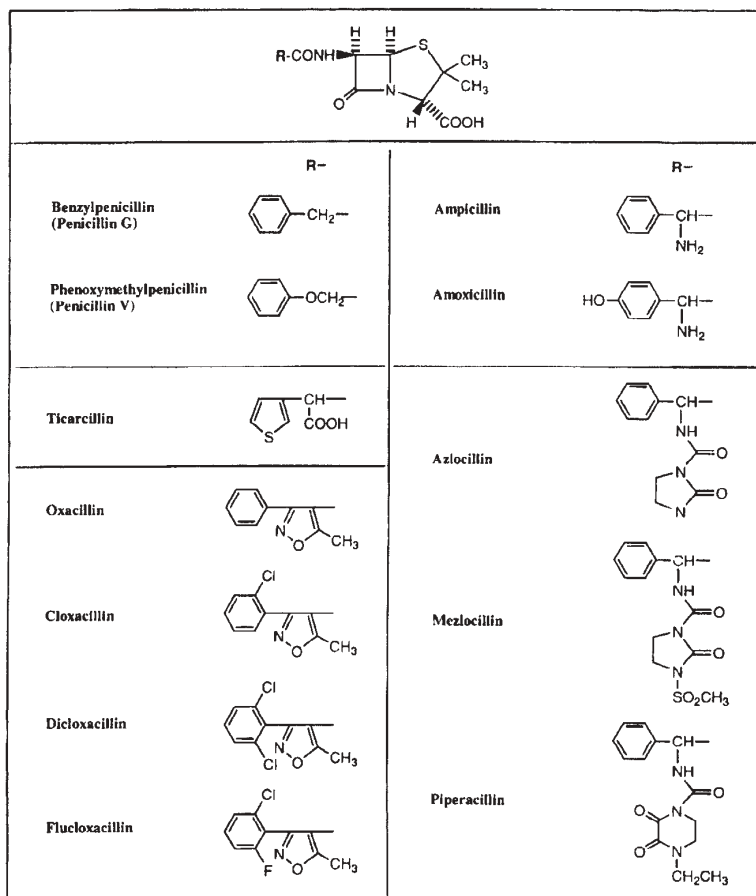
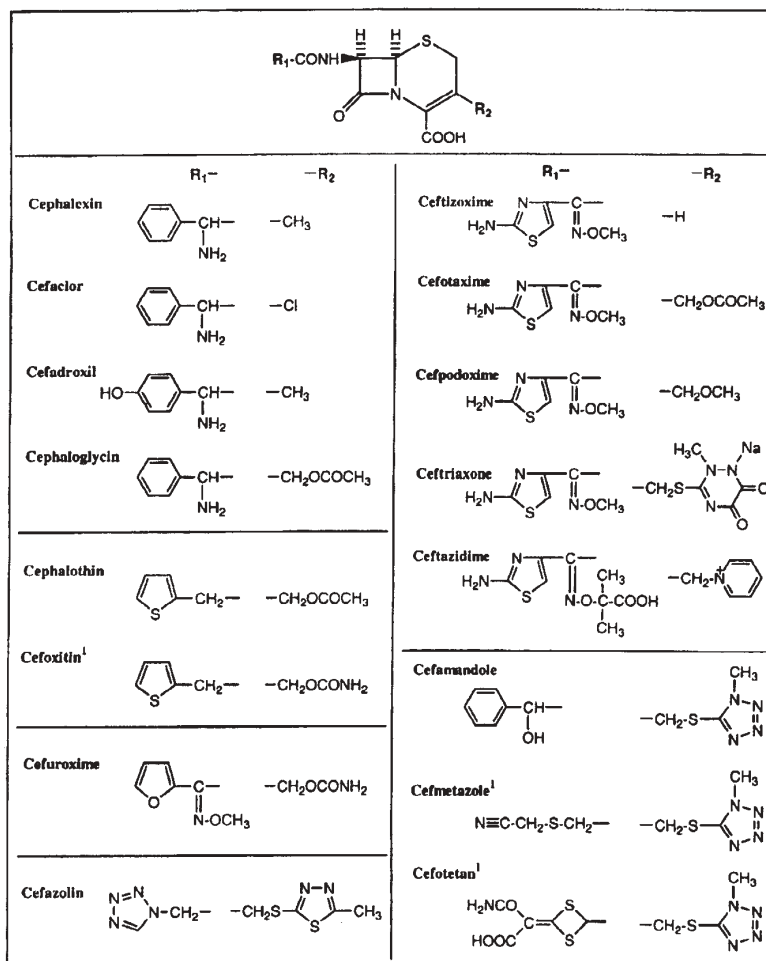


FIG 2. Structural similarities and differences of penicillin. From Baldo B. Penicillins and cephalosporins as allergens—structural aspects of recognition and cross-reactions. Clin Exp Allergy 1999;29:745. Used with permission.

In contrast to the penicillins, our understanding of the immunochemistry of the cephalosporins is even more limited. Thus, our knowledge of the relevant cephalosporin antigenic determinants is sparse, and for this reason their degree of cross-reactivity is unknown. Also, we are still unable to answer an important age-old question: Can penicillin-allergic patients safely receive cephalosporins? Although these two drug classes share a β -lactam ring (cephalosporins also have a unique dihydrothiazine ring), clinically relevant cross-reactivity is not common. Lin²⁴ found in a review of the literature that of 15,987 patients who were treated with cephaloridine, cephalexin, cephalothin, cefaxolin, or cefamandole, 8.1% of those with a history of penicillin allergy had reactions, versus 1.9% of persons who did not have such a history. More recently, Kelkar and Li²⁵ summarized all published studies that evaluated the risk of administering a cephalosporin to a penicillin-allergic patient. In 8 of the studies evaluated, penicillin skin testing was performed. In 3 of these studies, both persons who had positive skin test results and those who had negative skin test results underwent challenge; in 4, only those with positive skin test results underwent challenge, and in 1, only those with negative skin test results underwent challenge. Of

135 patients with positive skin test results who underwent challenge, 6 had reactions (reaction rate of 4.4%), whereas only 2 of 351 (reaction rate of 1.3%) patients with negative skin test results reacted. Although these data indicate that patients who have known penicillin-specific IgE antibodies may be at increased risk for a reaction to cephalosporins, other studies have shown that this risk is actually minimal.^{26,27}

Like the penicillins, cephalosporins too can induce immune responses. Side-chain-specific antibodies can be formed, as well as antibodies directed toward the ring structures. Thus, the principles of allergenic cross-reactions between cephalosporins are similar to those that pertain to the penicillins. If IgE antibodies are directed toward the core ring structures, cross-reactivity may exist among all the cephalosporins. If antibodies exist to the R1 or R2 side-chain group, however, the situation becomes much more complex. Cross-reactions may occur through R1 recognition of identical (cefazolin, cephalexin, cephaloglycin) or similar (cefazolin and cefadroxil) side-chains, or they may occur through R2 recognition (cephalothin and cefotaxime).²³ Current recommendations for patients with a demonstrated cephalosporin sensitivity are as follows. If a patient who has a history of a



¹ Cephamycin with an α -methoxy group ($-\text{OCH}_3$) at the 7-position

FIG 3. Structural similarities and differences of cephalosporins. From Baldo B. Penicillins and cephalosporins as allergens—structural aspects of recognition and cross-reactions. Clin Exp Allergy 1999;29:745. Used with permission.

cephalosporin allergy requires another cephalosporin, one of two approaches may be considered. (1) Perform a graded challenge with a cephalosporin that does not share side-chain determinants with the original cephalosporin. (2) Perform cephalosporin skin testing, although such skin testing is not standardized and the negative predictive value is unknown.²⁸ Fig 3 lists the various cephalosporins and their side-chain structural similarities.

In addition to IgE-mediated reactions, one cephalosporin, cefaclor, has been shown to cause a serum sickness-like syndrome. Because circulating immune complexes have not been found, these reactions are not considered to represent true serum sickness or immune complex reactions. Although the mechanism of these reactions is not clearly known, Kearns et al²⁹ have demonstrated that they may result from hepatic biotransformation of the parent drug.

Patients who have known or presumed IgE antibodies to a β -lactam drug may undergo desensitization if that drug is required for treatment. Acute drug desensitization involves the administration of incremental doses of a drug

over a period of hours to days and is a process whereby a drug-allergic person is converted from a drug-sensitive state to a state in which the drug is tolerated. Not only is the desensitized state antigen specific, it also is antigen dependent, requiring the continuous presence of antigen.

Penicillin desensitization is commonly performed, and either the oral or the intravenous route may be used. Once the starting dose has been determined,³⁰ drug doses are doubled every 15 minutes. Vital signs, the physical examination, and peak flow values are monitored throughout the procedure. Although most of our experience with drug desensitization has been derived from penicillin, this principle has been successfully applied to numerous other drugs as well.^{31,32}

Sulfonamides

A sulfonamide is any compound that contains a sulfonamide (SO_2NH_2) moiety. Sulfonamide antimicrobial agents are different from other sulfonamide-containing medications, such as furosemide, thiazide diuretics, and

celecoxib, by virtue of the presence of an aromatic amine at the N4 position, which is necessary for antibacterial activity. The presence of the aromatic amine allows sulfonamide agents to be placed into one of two groups, those that contain that contain aromatic amines (ie, sulfonamide antimicrobials) and those that do not. In addition to the aromatic amine, sulfonamide antimicrobials also contain a substituted ring at the N1 position. This group is not found in the nonaromatic amine-containing sulfonamides.

Reactions to sulfonamide antimicrobial agents are usually cutaneous in nature, and they occur in approximately 2% to 4% of healthy persons but in as many as 50% to 60% of patients with AIDS. The clinical reactions exhibited are diverse and include anaphylaxis, urticaria, erythroderma, fixed drug eruption, erythema multiforme, macular exanthems, and even more severe cutaneous reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Sulfonamides are metabolized in the liver by N-acetylation, yielding nontoxic metabolites, and by cytochrome P₄₅₀-catalyzed N-oxidation, yielding reactive hydroxylamines³³ that then oxidize to nitroso species.³⁴ These reactive nitroso metabolites are reduced by glutathione and then excreted. When the capacity for glutathione conjugation is exceeded, however, these metabolites may be directly cytotoxic, or through the formation of the N⁴-sulfonamidoyl hapten they may haptenate protein carriers, forming immunogenic complexes (Fig 4).^{33,35-37}

The fact that sulfonamide-induced reactions usually occur after several days of treatment suggests that an immune mechanism may be involved in at least some of the reactions demonstrated. More direct evidence of this involvement has come from studies that have demonstrated the presence of both specific T lymphocytes³⁸ and pro-inflammatory cytokines³⁹ in the involved skin of patients with sulfonamide-induced cutaneous reactions. In addition, IgE antibodies have been detected^{40,41} in patients reporting immediate-type hypersensitivity reactions to sulfamethoxazole.

At this time we have few diagnostic tools for evaluating patients with sulfonamide-induced reactions. Despite the fact that little is known about the mechanisms responsible for sulfonamide reactions in patients with AIDS, several "desensitization" protocols have been empirically developed and used, quite successfully, for these patients.⁴²⁻⁴⁸ The term "desensitization" is placed in quotation marks because in some instances the protocols that have been developed are more typical of a cautious graded challenge than of the rapid desensitization methods that are typically used in antibiotic desensitization. Several of the published protocols are listed in Table I. Desensitization protocols should not be attempted in patients who have had severe drug-induced cutaneous reactions, such as SJS or TEN.²⁸

Another important clinical problem with respect to sulfonamides is the degree of cross-reactivity between the sulfonamide antibiotics that have an arylamine group at the N4 position of the benzene ring and other sulfonamide derivatives (diuretics, sulfonylureas, celecoxib,

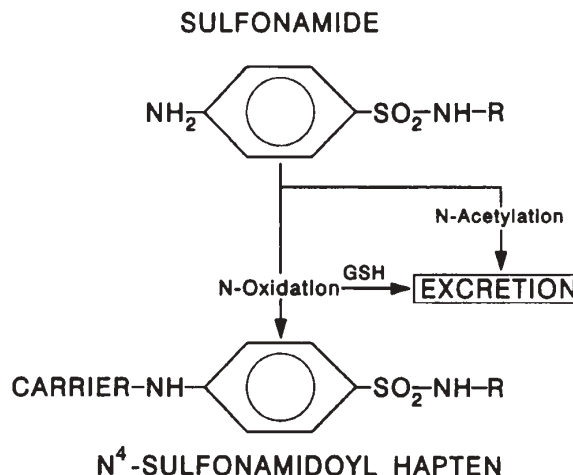


FIG 4. Sulfonamide metabolism. From Gruchalla R, Pesenko, RD, Do, TT, Skiest, DJ. Sulfonamide-induced reactions in patients with AIDS—the role of covalent protein haptenation. *J Allergy Clin Immunol* 1998;101:372. Used with permission.

dorzolamide, sumatriptan) that do not have this group. It appears that cross-reactivity between sulfonamide antibiotics and these other sulfonamide drugs is theoretical only. Despite this, however, the Physicians Desk Reference (2002) cautions against the use of some of these agents in patients with a history of a sulfonamide allergy. Allen⁴⁹ summarized the product labeling advice for various sulfonamide drugs with regard to their use in patients with a history of sulfonamide allergy. This information is presented in Table II.

Other antimicrobial agents

Unfortunately, little is known about the mechanisms responsible for most antimicrobial reactions. Although most of these reactions are not immunologically mediated, some of them most certainly are. Reactions consistent with an IgE-mediated mechanism, such as urticaria, angioedema, and anaphylaxis, are typically easy to recognize. Because there are no valid skin testing reagents available to confirm the presence of drug-specific IgE antibodies, however, we are currently unable to prove their existence and thus confirm the diagnosis. The more nonspecific drug eruptions are even more problematic. Not only are the mechanisms responsible for many of these reactions not known, but also the drug determinants responsible for their elicitation have in most cases not been identified. For these reasons, we have few in vivo or in vitro diagnostic tests for drug allergy.⁵⁰

Despite our limited tools and knowledge, for those antimicrobial reactions that are presumed to be IgE mediated, skin testing with the native drug may provide some useful information.^{51,52} Because the native drug may not contain all the relevant antigenic determinants that may elicit IgE-mediated reactions, a negative skin test result must be interpreted with caution. In contrast, a positive skin test result may be extremely helpful. If the dose used to elicit the positive wheal and flare response does not elicit an irritant response in a healthy control

TABLE I. Sulfonamide desensitization protocols for patients with AIDS

Study	Desensitization procedure	Indication	Outcome and comments
Absar et al, ⁴² 1994	10 d	PCP prophylaxis, isosporiasis	23/27 successfully desensitized
Moreno et al, ⁴³ 1995	TMP-SMX, 8 h; sulfadiazine, 2.5 h	Central nervous system toxoplasmosis, nocardiosis, isosporiasis	1/2 TMP-SMX and 7/11 sulfadiazine desensitizations successful; of 8 successfully desensitized, 6 were premedicated
Palusci et al, ⁴⁴ 1996	4 h	PCP or PCP prophylaxis	5 children and infants with IgE-mediated reaction to TMP-SMX evaluated; 3/5 successfully desensitized
Caumes et al, ⁴⁵ 1997	3 d	PCP prophylaxis	37/48 successfully desensitized; factors predictive of failure were higher CD4 ⁺ cell percentage and higher CD4 ⁺ /CD8 ⁺ ratio
Rich et al, ⁴⁶ 1997	8 d	PCP prophylaxis	18/22 successfully desensitized
Demoly et al, ⁴⁷ 1998	6 h	PCP prophylaxis	44/44 successfully desensitized on day of procedure; overall success rate at 1 mo 91% (40/44)
Yoshizawa et al, ⁴⁸ 2000	5 d	PCP prophylaxis	15/17 patients successfully desensitized

PCP, *Pneumocystis carinii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE II. Use of sulfonamide-containing drugs in patients with a history of sulfonamide allergy

Drug	Product labeling advice for use in sulfonamide allergy	Comments
Acetazolamide (Diamox)	None	One case report of cross-reactivity in 1955
Amprenavir (Agenerase)	Caution advised	—
Brinzolamide (Azopt)	None	Labeling warns that because brinzolamide is a sulfonamide with systemic absorption, serious allergic reactions are possible
Bumetanide (Bumex)	None	Labeling notes sulfonamide-allergic patients may be allergic to bumetanide
Captopril (Capoten)	None	Not a sulfonamide; no concerns about use
Celecoxib (Celebrex)	Contraindicated	—
Chlorpropamide	None	—
Chlorthalidone	Contraindicated	—
Chlorothiazide (Diuril)	Contraindicated	—
Dorzolamide (Trusopt)	None	Labeling warns that because dorzolamide is a sulfonamide with systemic absorption, serious allergic reactions are possible
Furosemide (Lasix)	Caution advised	—
Glipizide (Glucotrol)	None	—
Glyburide (DiaBeta)	None	A few postmarketing reports of cross-reactivity
Hydrochlorothiazide (HydroDiuril)	Contraindicated	—
Indapamide (Lozol)	None	—
Metolazone (Zaroxolyn)	None	Cross-sensitivity has not been reported but is a theoretical concern
Rofecoxib (Vioxx)	None	Not a sulfonamide; no concerns about use

From Allen J. Which medications to avoid in patients with sulfa allergy. Stockton (CA): Pharmacist's Letter and Prescriber's Letter; 2000. Used with permission.

subject, then it can be presumed that the positive skin test response is due to the presence of drug-specific IgE antibodies. It is important to realize that when skin testing is performed with intravenous antibiotic formulations, some antibiotics produce marked irritant responses if they are not extensively diluted.⁵²

IMMUNE REACTIONS TO NONANTIMICROBIAL DRUGS

Anticonvulsants

Phenytoin, phenobarbital, and carbamazepine are known to cause a severe hypersensitivity syndrome (HSS)

that consists of fever, rash, lymphadenopathy, and differing degrees of internal organ involvement. Typically the symptoms begin several weeks into therapy. The rash, which initially is often a benign morbilliform eruption, may develop into frank exfoliative dermatitis. Because this syndrome is oftentimes associated with eosinophilia and systemic symptoms, it is also termed *drug reaction with eosinophilia and systemic symptoms* (DRESS). Other drugs, in addition to the anticonvulsants, that have been associated with this syndrome, include dapsone and the sulfonamides, allopurinol, and minocycline.

Recently, data supporting the involvement of an immune mechanism in this syndrome have been accu-

TABLE III. Criteria used in the classification of severe drug eruptions

	SJS	TEN	HSS/DRESS
Mucous membrane	>90%	>90%	<30%
Erosions	Several sites	Several sites	Mouth and lips
Detachment of epidermis	Yes, <10% BSA*	Yes, ≥30% BSA*	No
Hyperkeratosis, desquamation	No	No	Usual
Neutropenia	No	30%	No
Eosinophilia	No	No	90%
Atypical lymphocytes	No	No	30%-40%
Respiratory tract	Bronchial erosions, ARDS	Bronchial erosions, ARDS	Interstitial pneumonitis
Liver	Hepatitis 10%	Hepatitis 10%	Hepatitis 60%
Heart	No	No	Myocarditis
Lymph node enlargement	No	No	Usual

From Bachot N, Roujeau J-C. Pathophysiology and treatment of severe drug eruptions. *Curr Opin Allergy Clin Immunol* 2001;1:293-8. Used with permission. BSA, Body surface area; ARDS, adult respiratory distress syndrome.

*When detachment involves 10% to 29% of BSA, case is classified as SJS-TEN overlap.

mulating. The fact that an induction period appears to be required during the first course of treatment only but not after subsequent exposures supports the involvement of an immune mechanism.

The aromatic anticonvulsants are metabolized in part by cytochrome P₄₅₀ enzymes to reactive arene oxide metabolites, and it is thought that these metabolites may be responsible for the pathologic process demonstrated in drug-induced HSS.⁵³ Defective detoxification may lead to excessive formation of arene oxides, which may then contribute to the disease process either through direct cellular necrosis or through the generation of an immune response after haptenation of protein carriers.

Treatment of HSS is similar to the treatment of other severe drug eruptions and is basically supportive. First and foremost, the causative agent should be rapidly withdrawn. For patients who have a marked exfoliative dermatitis, treatment often requires specialized care in intensive care units or in burn units. The main goals of care are similar to those for patients with burns and other similar severe drug-induced reactions (eg, SJS and TEN) and include volume replacement, antibiotics, nutritional support, warming of the environment, and extensive skin care. Corticosteroids may be administered if symptoms are severe. Although there have been case reports of dramatic improvement of visceral manifestations of HSS or DRESS after administration of moderate to high systemic doses of steroids, relapses have been seen to occur when steroids are tapered.⁵⁴ Table III compares and contrasts the characteristics of the most common severe drug-induced cutaneous eruptions.

Cross-reactivity rates among the aromatic anticonvulsants may be as high as 75%. Patients who have had HSS or DRESS should avoid all aromatic anticonvulsants. For these patients potential alternative drugs are valproic acid (not in the acute phase because of the risk of hepatitis), gabapentin, vigabatrin, and benzodiazepines.⁵⁵ There is no evidence that cross-reactivity exists between lamotrigine and the aromatic anticonvulsants. However, this agent too has been associated with HSS, as well as with TEN and SJS. Also, because there is a familial tendency toward hypersensitivity to anticonvulsants, family counseling is an important component of patient management.⁵⁵

Chemotherapy agents

Hypersensitivity reactions have been reported for all chemotherapeutic agents in use. However, the most common agents that elicit such reactions are the taxanes, platinum compounds, asparaginases, and epipodophyllotoxins. Reactions range from mild cutaneous eruptions to respiratory arrest, cardiac collapse, and even death.

In the chemotherapy literature, the term *hypersensitivity reaction* is often used. However, convincing supporting mechanistic data often is not provided. Because many of the associated reactions consist of flushing, heart rate and blood pressure changes, bronchospasm, and pruritus, it is thought that these reactions may be mediated by an immediate-type hypersensitivity mechanism. Because some of these agents or their excipients may elicit mast cell mediator release directly, however, nonimmunologic mechanisms probably account for at least some of these reactions.

The taxane paclitaxel is used to treat lung, breast, and gynecologic malignancies. Docetaxel, its sister agent, is a newer semisynthetic taxane. In the early phase I and phase II studies of the taxanes, as many as 42% of patients who received paclitaxel had a so-called "hypersensitivity" reaction, and 2% of these were severe.⁵⁶ Most reactions occur during first exposure, and they consist of dyspnea or bronchospasm, urticaria, flushing, hypotension, and angioedema. Although these symptoms are consistent with an IgE-mediated mechanism, there is no period of sensitization, so the more likely mechanism is direct mast cell degranulation. In the case of paclitaxel reactions, the induced reactions may be due to the drug's excipient, Cremophor EL, a nonionic surfactant derived from castor oil that has been shown to lead to histamine release and hypotension in dogs.⁵⁷ Another taxane, docetaxel, is also associated with a high incidence of reactions yet does not contain Cremophor EL, however, so it is likely that the taxane moiety may be the etiologic agent responsible for these reactions.

Prophylaxis is routinely done before taxane administration because of its effectiveness in reducing the incidence and severity of paclitaxel- and docetaxel-induced

“hypersensitivity” reactions.⁵⁶ Essentially all patients who have “hypersensitivity” reactions to paclitaxel or docetaxel are able to undergo successful retreatment again, as long as they are pretreated with antihistamines and corticosteroids.⁵⁸ For patients who have recurrent reactions despite premedication, a desensitization protocol has been developed.⁵⁸

The platinum compounds, both cisplatin and carboplatin, commonly induce hypersensitivity reactions. Unlike with the taxanes, however, a period of exposure (several courses of drug administration) is required before a reaction, typically anaphylactic, is elicited. Thus, these reactions may be truly immunologic in nature. Skin testing has been used to identify patients at risk for development of reactions, and a negative test result has been shown to have an extremely high (96%) negative predictive value.⁵⁹ Desensitization protocols have been developed for patients with positive skin test results, but these have not been uniformly successful.^{58,60,61}

Asparaginase, a bacterial (from *Escherichia coli*) polypeptide protease that depletes tumor cells of asparagine, is used for treatment of acute lymphoblastic leukemia. Approximately 25% to 35% of patients who receive this agent have a hypersensitivity reaction that consists of anaphylactoid symptoms.⁶² Most patients require repeated exposure before a reaction develops, and anti-asparaginase antibodies have been found in some persons.⁶³ Intradermal testing is generally performed before initial administration of asparaginase and before subsequent doses if a week or more has elapsed since the previous dose.⁶⁴

Several additional asparaginase preparations (*Erwinia carotovora* asparaginase and polyethylene glycol–modified *E coli* asparaginase) have been developed, and these may be used to treat persons who have had asparaginase-induced reactions. Although a rapid desensitization protocol for asparaginase hypersensitivity has been published,⁶⁵ this procedure is not used routinely.

The epipodophyllotoxins etoposide and teniposide are antimetabolic agents that are used in the treatment of testicular and ovarian germ cell tumors, small cell lung carcinomas, non-Hodgkin lymphomas, and many other cancers. The incidence of etoposide- and teniposide-induced reactions ranges from 6% to 41%, and there is a 0.7% to 14% incidence of anaphylaxis.^{66,67} Reactions typically consist of fever, chills, hypotension, dyspnea, and bronchospasm. Because some of these reactions occur with the first dose, it is not clear that they are immunologically mediated. Rather these agents, like paclitaxel, may cause direct mast-cell mediator release. There are no standard prophylaxis regimens, and fewer than half of those who have a drug-induced reaction are able to tolerate the drug on readministration.^{64,66}

Heparin

Heparin, a mucopolysaccharide with a molecular weight of 6000 d to 20,000 d, can elicit several types of immunologically mediated reactions, such as urticaria, asthma, anaphylaxis,⁶⁸ delayed cutaneous eruptions (ery-

thematous plaques and skin necrosis), and heparin-associated thrombocytopenia II. The mild thrombocytopenia that is noted with heparin therapy is probably not immunologically mediated and is reversible after the drug is discontinued.⁶⁸ However, the more severe sudden and massive thrombocytopenia, thrombosis, and necrosis seen after about 5 days of treatment are due to immune complexes composed of heparin-dependent IgG antibodies specific for platelet factor 4.

Additional antithrombotic agents have been developed, including the low-molecular weight heparins (enoxaparin [Lovenox] and dalteparin [Fragmin]), danaparoid sodium (Orgaran), and the direct thrombin inhibitors argatroban and lepirudin (Refludan, a hirudin). Skin testing does not appear to be useful in evaluating immediate-type hypersensitivity responses to heparin. However, positive delayed cutaneous skin test responses have been demonstrated in patients who have erythematous plaques develop at heparin injection sites.^{69,70} In addition, it has been shown that patients who have positive delayed skin test responses also frequently have “heparin-induced” IgG antibodies. Because cross-reactivity has been demonstrated between heparin, the low-molecular weight heparins, and danaparoid sodium, it is recommended that the new alternative direct thrombin inhibitors be used in patients allergic to heparin.^{69,71}

Insulin and protamine

Reactions to insulin therapy have occurred since the introduction of animal insulin in 1922. With the introduction of recombinant human insulin (Humalog), however, the incidence of insulin-induced allergic reactions has decreased. Although the most common insulin-induced reactions are local reactions at the injection site, systemic reactions may occur as well, although they are rare. IgE antibodies have been demonstrated in both types of reaction.^{72,73} Some local reactions may be controlled by premedication with antihistamines or corticosteroids.⁷² For patients who do not have a response with this approach, subcutaneous insulin infusion may be beneficial.⁷² For patients who have had systemic reactions, desensitization has been successful.⁷³

Reactions to protamine-containing insulins may be caused by the protamine component in the insulin preparation and not by the insulin itself. Protamine sulfate is a low-molecular weight polycationic protein that is used to reverse the anticoagulant properties of heparin, and it is also complexed to insulin (neutral protamine Hagedorn insulin) to delay absorption. Dykewicz et al⁷⁴ reported on two patients with diabetes who had anaphylaxis in response to neutral protamine Hagedorn human insulin but who tolerated regular insulin. Both patients had negative skin test reactions to regular insulin but positive reactions to neutral protamine Hagedorn insulin and to protamine, indicating that protamine-specific IgE antibodies were responsible for the anaphylactic reactions. Because it has been shown that patients with diabetes who receive protamine-containing insulins are at a much greater risk for development of anaphylaxis in response

to intravenous protamine, these patients should be carefully evaluated before the performance of cardiopulmonary bypass procedures that involve that agent.

Biologic response modifiers

Biologic and other novel therapies that target specific pathogenic processes are being developed at a rapid rate. These agents provide new therapeutic options for patients with chronic debilitating diseases. New immunomodulators include interferons, TNF- α inhibitors, growth factors, monoclonal antibodies that inhibit T- and B-cell activation, complement protein inhibitors, and many other agents. Although many of these agents have been shown to have therapeutic benefits, adverse reactions, some of which may be immunologic, are not uncommon.

General symptoms that have been seen include fever, chills, and malaise, but more severe reactions may be seen with specific agents. Among the more mild reactions, injection site reactions are the most common. These have been demonstrated with both the interferons and TNF- α inhibitors. In a recent retrospective study that evaluated the incidence of injection site reactions in patients receiving the TNF- α inhibitor etanercept, 20% of treated patients reported reactions within the first 2 months of therapy. These reactions were characterized by an inflammatory infiltrate that consisted of predominantly activated mature cytotoxic T lymphocytes, but interestingly they waned overtime.⁷⁵

As more and more biologic response modifiers are developed, further investigation will be necessary to better understand the nature of the adverse reactions that occur with their administration. Some of these most certainly will be immunologic in nature. Not only will it be important to identify the antigenic stimulus responsible for these immunologically mediated reactions, but also tests that predict their occurrence should be developed.

ASPIRIN AND OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Most reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are nonimmunologically mediated. However, some anaphylactoid reactions to aspirin and NSAIDs have features that are consistent with IgE-mediated reactions (they occur after two or more exposures to aspirin, and they are specific to one NSAID only). To date, however, aspirin-specific IgE antibodies have only rarely been demonstrated. For patients with aspirin-sensitive asthma, a recent study demonstrated that one of the new cyclooxygenase 2 inhibitors, rofecoxib, is well tolerated.⁷⁶ For an overview of aspirin- and NSAID-induced reactions, see the 1998 review by Stevenson and Simon.⁷⁷

NONIMMUNOLOGIC DRUG REACTIONS

Reactions to angiotensin-converting enzyme inhibitors, local anesthetics, NSAIDs, opioid antagonists, and radio-contrast media are not immunologically mediated in most instances. They therefore are not discussed in this article.

MANAGEMENT OF THE PATIENT WITH DRUG ALLERGY

Currently, there are few tools available to help us in the evaluation and management of patients who are seen with drug-induced reactions. These tools do not yet exist, because we have limited knowledge of the pathophysiology and factors that predispose toward the development of most of these reactions. Despite these inadequacies, patients must be managed.

The approach to the drug-allergic patient must be methodic. First, a drug-disease connection must be established. Once this has been done, the reaction type must be determined if at all possible. For reactions in the type A category, dosage modification may be all that is necessary before drug readministration. Toxicity, as well as drug-induced side effects and secondary effects, may resolve at lower drug dosages.

For type B drug intolerance-type reactions, the implicated drug may be readministered if the previous reaction was mild (eg, tinnitus with aspirin). For idiosyncratic reactions, however, more caution is advised. For severe or life-threatening reactions, the drug should not be readministered. For less severe reactions, however, a provocative challenge may be considered.

For type B immunologically mediated reactions, the management option depends on the mechanism responsible for the reaction. If confirmatory tests are available and they have been validated, these tests should be used to determine the allergic status of the patient (eg, testing for penicillin-specific IgE antibodies with Pre-Pen and minor determinant mixture). When such tests are not available, however, and in most cases they are not, several approaches can be taken. The simplest approach is to avoid the drug if an alternative agent is available. If an alternative drug does not exist, a graded challenge with the implicated agent can be done if the previous reaction was not consistent with an IgE-mediated reaction, and it was not life-threatening. If the previous reaction was consistent with an IgE-mediated reaction, however, then desensitization should be considered.

CONCLUSIONS

In addition to educating patients about their drug reactions, it is imperative that allergists educate the primary care physicians caring for these patients, as well. Most drug-induced reactions are nonallergic in nature. Both the patient and the referring physician must be made aware of this fact. All too often the referring physician terrifies the patient by stating that, in light of the patient's multiple drug "allergies," few treatment options exist. It is no wonder that, in the case of antibiotic reactions, the patient believes that he or she is doomed should an infection arise. As stated in this review, options, though limited, do exist. It must be remembered, however, that both time and patience are needed to develop the optimal treatment approach.

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