

## Hypersensitivity Reactions to Drugs: Evaluation and Management

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### Abstract

Most hypersensitivity reactions to drugs occur within several weeks of administration; signs and symptoms are often consistent with known immune-mediated reactions, including anaphylaxis, rashes, fever, cytopenias and vasculitis. The culprit immune mechanisms range from immunoglobulin E antibody to T cells inducing apoptosis of keratinocytes, in the case of bullous exfoliative rashes. Many drugs induce reactions via altered hepatic metabolism, with production of reactive intermediates which induce a common syndrome of rash and fever plus variable types of other signs. Examples of this "reactive metabolite syndrome" include the rash and fever in HIV-positive patients given sulfamethoxazole and reactions to the aromatic anticonvulsants. With the notable exception of anaphylaxis and severe bullous exfoliative rashes, most immune reactions to drugs are not life-threatening and generally resolve once the drug is discontinued. The key is prevention. Specific immune testing is standardized only for penicillin. If test results are negative, however, the patient can tolerate all beta-lactam antibiotics. Of those patients with a positive penicillin skin test, only 2% develop reactions when given cephalosporins. Sulfa and quinolone antibiotics, and muscle relaxants, also frequently induce reactions. If there is a history of bullous rash, the patient should never again receive sulfa or quinolone, or related drugs. In other cases, a cautious graded challenge or desensitization can be done.

Vancomycin, protamine, and radiocontrast media induce non-immune reactions secondary to their irritant effects on vascular endothelium. Narcotic pain medications cause histamine release by binding to a specific receptor on mast cells in sensitive patients. In contrast to true immune reactions, most patients can receive these medications again, if they are pretreated and the drugs are given slowly. Angiotensin-converting enzymes, aspirin, and non-steroidal anti-inflammatory drugs induce adverse reactions by their effect on enzymes. Readministration usually results in repeat symptoms. It is possible to desensitize patients to aspirin. Some patients appear to develop similar adverse symptoms with multiple unrelated drugs. Although these cases present management problems, most patients can complete a therapeutic course of a vital drug, after careful review of the history, immune testing when possible, and graded challenge or desensitization.

**Key Words:** Drug allergy, drug hypersensitivity, allergy to antibiotics, drug rashes, hypersensitivity to beta-lactam antibiotics, hypersensitivity to sulfa drugs, mechanisms of drug allergy, signs and symptoms of drug hypersensitivity.

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### Introduction

MANY PATIENTS experience hypersensitivity reactions to drugs. Only a small percent of these reactions are truly "allergic," i.e., the immune system specifically reacts to the drug, com-

monly with production of a specific antibody or sensitized T cells. Other reactions are the result of non-immune mechanisms, including altered hepatic metabolism, direct irritation of vascular endothelium, or interaction with enzymes.

A common problem encountered by physicians is the presentation of a patient on multiple drugs, with unpredictable signs or symptoms, thus raising the possibility of a hypersensitivity reaction. The first question that should be asked in this setting is whether the signs and symptoms are consistent with known immune-mediated reactions. These are discussed in detail below. If so, the next step is to evaluate the drugs the patient is taking. Most immune-mediated reactions to drugs occur within the first few weeks of administration. Since many patients, especially those who are hospitalized,

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Adapted from a Grand Rounds presentation to Department of Medicine, Mount Sinai School of Medicine, New York, NY, on December 12, 2000, and updated as of July 3, 2002.

are commonly on multiple drugs, several may be implicated as possible causes of the reaction. Patients also need to be questioned thoroughly about their intake of non-prescription products. One needs to know the propensity of these medications to stimulate the immune system. Drugs such as penicillin have chemically reactive metabolites which covalently bind to body proteins; these are more potent antigens than macrolide antibiotics, which have less chemically reactive metabolites, and other drugs.

### Anaphylaxis

Common signs and symptoms of allergic drug reactions are noted in Table 1. The only life-threatening reaction other than toxic epidermal necrosis is anaphylaxis. Patients at risk of anaphylaxis have increased amounts of immunoglobulin E (IgE) antibody specific for the drug. IgE is attached to receptors on mast cells and basophils. Administration of the first therapeutic dose of the drug binds with this antibody; this induces an explosive release of mediators from the cell. The resultant signs and symptoms of anaphylaxis are predominantly due to histamine, although at least 15 other active chemicals are also released, such as prostaglandin D<sub>2</sub> and leukotriene C<sub>4</sub>, which induce bronchoconstriction; cytokines IL-4 and 13, which increase IgE production; and tumor necrosis factor alpha (TNF $\alpha$ ), a key cytokine in allergic inflammation. The clinical presentation is usually flushing, pruritus, urticaria, angioedema, bronchoconstriction and/or hypotension. Rarely, women may present with intense uterine cramping.

Epinephrine must be administered emergently to treat anaphylaxis. Appropriate fluids should be administered intravenously to restore intravascular volume. Antihistamines work by competitively binding to histamine receptors, thereby preventing manifestations of histamine release; they do nothing for an anaphylactic reaction, where histamine release has already occurred and symptoms are apparent. Steroids, likewise, are therapeutically ineffective for the immediate reaction.

The great majority of anaphylactic reactions occur within one hour of drug administration, while some of the reactions may occur later, within two hours (1). If a drug is subsequently administered according to its dosing interval, there should be no further risk of anaphylaxis beyond the first dose. Patients on beta-blocker (1) or angiotensin II inhibitors (2) may be at risk of more severe reactions.

### Urticaria and Angioedema

Urticaria and angioedema are generally due to IgE antibody and can occur at any time during a course of drug administration. If a patient has sufficient IgE antibody prior to administration of the drug, urticaria and angioedema will commonly occur as part of anaphylaxis in the first one to two hours. In many cases, however, the patient does not have specific IgE antibody, or sufficient amounts of it, to induce an immediate reaction. In these cases, the immune system may turn on immediately, or days later, with stimulation of T cells inducing B cells to change to plasma cells and produce IgE. If the drug is administered on a regular schedule, the small initial amounts of new IgE will immedi-

**TABLE 1**  
*Signs and Symptoms Commonly Associated with Allergic Drug Reactions*

Signs and Symptoms	Immune Mechanism
Anaphylaxis	IgE antibody
Urticaria and angioedema	IgE antibody
Rashes – macular-papular – vesicular exfoliative	cytotoxic T cells kill keratinocytes expressing MHC II + drug ? CD8+ T cells induce lysis of keratinocytes
Fever	? release of cytokines
Immune complex reactions (rash, fever, arthralgias, myalgias, lymphadenopathy, nephritis, vasculitis)	IgG and IgM antibodies
Cytopenias	IgG and IgM antibodies

ately bind the drug, with resultant urticaria, starting slowly and increasing. If this occurs, the drug should be stopped, as IgE production will continue to increase.

Treatment of urticaria and angioedema consists of stopping the suspect drug and starting an antihistamine. The once-a-day preparations are usually effective. Occasionally, steroids may be necessary. Urticaria may persist beyond the half-life of the drug. This is probably due to the persistence of small amounts of tissue-bound drug.

### **Morbilloform Drug Rashes**

The most common manifestation of an allergic reaction to a drug is a non-urticarial rash. Recent data suggest that there are two distinct types of rashes with different immune pathogenesis and prognosis: morbilliform or macular-papular and bullous. Morbilliform rashes are the most frequent immune reaction to drugs, occurring in approximately 2% of cases. Macules and papules of varying sizes, usually pruritic, occur symmetrically, commonly starting on the trunk, with eventual spread to the terminal extremities. Sometimes the face is spared. Onset varies from days to 1–2 weeks after initial administration of the drug. In some cases, the onset may occur after the drug has been discontinued. In these cases, residual tissue-bound drug can sometimes provide sufficient antigen to induce clinical symptoms for 1–2 weeks.

The pathogenesis is not clear, but most likely is mediated by cytotoxic T cells. Drugs can bind to major histocompatibility complex (MHC) class II antigens expressed on keratinocytes; T cells will then bind to the drug, thus inducing the T cell to release inflammatory cytokines, with resultant lysis of the keratinocytes (3, 4). There is limited research in this area, in part because it is clearly difficult to set up prospective studies, and because the rash, while uncomfortable, is rarely clinically significant. At worst, patients may experience epidermal peeling, similar to a bad sunburn. Treatment consists of stopping the drug, although sometimes it is possible to continue the treatment even when a rash occurs. This should only be done under the guidance of a physician familiar with drug rashes. If necessary, steroids (e.g., prednisone 30 mg on taper) may hasten resolution.

Uniquely, the aminopenicillins (e.g., ampicillin and amoxicillin) are associated with a high frequency of morbilliform rashes, up to 10% per course (5). If a patient has concurrent infectious mononucleosis, the frequency is 95% (6) to

100% (7). The mechanism is unknown, but there is no evidence of specific antibody. Immune responses to viral infections usually result in increased levels of interleukin 5 (IL5) which will upregulate expression of MHC class II antigens on keratinocytes. If the drug binds to MHC class II antigens, T cells can recognize the bound drug directly (4). Patients with a history of a rash coincident with an aminopenicillin have a higher frequency of certain major histocompatibility genes than do non-reactors (8). If the drug is continued, some rashes may clear spontaneously. In most cases, patients tolerate readministration of an aminopenicillin without incident (9). If the physician is sure that the past rash was morbilliform, patients can be rechallenged with any beta-lactam antibiotic. If, however, there is *any* question that the previous rash was urticarial, then there is the possibility of IgE involvement, and the patient must undergo skin testing, as discussed below, before any future beta-lactam antibiotic is administered.

### **Bullous Exfoliative Drug Rashes**

The above-mentioned morbilliform rashes differ from blistering-exfoliative rashes, which appear to have a distinct immune pathogenesis. Although there is some disagreement, many physicians now categorize these rashes on a spectrum from minor to severe. Erythema multiforme minor is characterized by indurated lesions, at times bullous and often target shaped, with inner and outer red rings. Erythema multiforme major (also known as Stevens-Johnson syndrome) is the same rash, with systemic symptoms of fever and mucous membrane involvement, most commonly of the mouth or conjunctiva. Toxic epidermal necrolysis may be slightly different, as biopsies show necrosis of the “full” thickness of the epidermis, but most physicians consider it part of this spectrum, and it is generally defined as bullous rash involving more than 30% of the skin. The exact pathogenesis remains to be determined, but appears to involve activation of T cells which induce necrosis of epidermal cells (10). Sulfonamides account for the majority of drug-related episodes; however, it is a rare problem with a risk of 4.5 cases per million exposed persons per week (11). If there is any suspicion of a vesicular-exfoliative rash, the drug should be stopped immediately and the patient should be advised never to take that drug or one that is related.

Treatment of vesicular-exfoliative rashes is controversial. The mortality of toxic epidermal

necrolysis used to approach 40%, as patients presented the same clinical management problems as severe burn patients, with loss of epidermis and subsequent fluid and infection problems. One paper suggested that steroid treatment is detrimental, since the mortality in the treated group was higher than in the untreated group (12). As a result, many physicians feel steroids are contraindicated for toxic epidermal necrolysis. Others, however, including this author, have used steroids with remarkable success for erythema multiforme major (13). Some anecdotal reports claim excellent results following the use of other immunosuppressants, including cyclosporin and tacrolimus. Most physicians now agree that steroids should be started at the first sign of a vesicular-exfoliative rash. High doses should be used initially, e.g., prednisone 60 mg, and then the dose should be tapered.

### **Drug Fever**

Fever is also a manifestation of an immune reaction to a drug, but is often not considered in the differential diagnosis. If the suspect drug is stopped, the majority of patients will defervesce in 24 hours, and almost all by 48 hours (14). There is no characteristic fever pattern; shaking chills may occur, although there is a tendency for the patients to look better than one would expect with high fever from an infectious source. There is also no characteristic laboratory abnormality. The time between start of drug and onset of fever is variable, with a mean of 21 days and a median of 8 days (14). The immune mechanism is not clear, but is most consistent with release of pyrogenic cytokines, e.g., TNF $\alpha$  and IL1, from antigen-processing cells such as macrophages. Because there appears to be no other specific immune response, rechallenge appears safe, with immediate recurrent fever as the only manifestation (14).

### **Immune Complex Reactions**

Drug allergy may also involve the production of specific IgG and IgM antibodies. The immune complexes of drug plus antibody, in slight antigen excess, can pass through the endothelial lining of blood vessels. In the tissue, they induce inflammation, in part because of complement activation. Depending on where they filter out, the clinical presentation can range from vasculitis with palpable purpura on the skin, to arthralgias, myalgias or nephritis.

Complexes can also attach to blood cells, inducing cytopenias. Commonly, symptoms of immune complex disease appear after 7–10 days of drug administration. It takes that long for adequate amounts of antibody to be formed in order to create complexes of slight antigen excess. Generally, it is a self-limiting problem; if the drug continues to be administered, antibody production continues and complexes become larger, with antibody excess. The larger complexes are too big to pass through endothelial lining and are cleared by the reticular endothelial system. If treatment is necessary, prednisone 30 mg or equivalent, tapered pending symptoms, is usually sufficient.

### **Drug Hypersensitivity Due to Altered Hepatic Metabolism: The Reactive Metabolite Syndrome**

Other reactions to drugs do not involve the classic mechanisms discussed above, but are a result of the altered hepatic metabolism of drugs, with production of reactive intermediate metabolic products (15). Examples of reactions due to altered hepatic metabolism include: the rash and fever associated with sulfamethoxazole in HIV-positive patients (16, 17); cefaclor and probably cefprozil “serum-sickness-like” reactions (18, 19); the fever, rash and lymphadenopathy reactions to the aromatic anticonvulsants which produce arene oxide (e.g., phenytoin, carbamazepine or phenobarbital) (20); and “lupus-like” reactions from prolonged treatment with procainamide (21).

Most drugs are metabolized in the liver by acetylation, hydroxylation, or glucuronidation, with the production of nontoxic metabolites. Some drugs, however, are selectively or partially metabolized by the cytochrome P450 system, with the production of reactive intermediates, such as sulfamethoxazole-hydroxylamine in the case of sulfamethoxazole. Most reactive metabolites are rapidly detoxified by enzymes, which may not be as active or efficient in patients who develop adverse reactions. In the case of the anticonvulsants, the toxic intermediate products are arene oxide metabolites. Anticonvulsant hypersensitivity syndrome seems to be associated with an inherited deficiency of epoxide hydrolase, the enzyme responsible for metabolizing these intermediate products (20). Some first-degree relatives of patients who have had reactions to cefaclor and the aromatic anticonvulsants also have altered hepatic metabolism of the same drugs (22). Patients should

therefore be asked if relatives have experienced adverse reactions to these or other drugs. In the case of HIV-positive patients, some have been noted to be deficient in glutathione, which enhances metabolism of the reactive metabolite of sulfa (23). Some patients may be slow acetylators; therefore, an increased amount of drug is metabolized instead by the cytochrome system. This has been noted in 90% of HIV patients versus 55% of age-matched controls (24).

Six cytochrome isoenzymes are responsible for most drug metabolism. These are cytochromes 1, 2, and 3 with the respective isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. 3A4 is the most abundant and accounts for the largest percent of drug metabolism (25). Theoretically, a patient might have abnormal metabolism via one isoenzyme and therefore react to other drugs metabolized by this route. Interaction between drugs which competitively bind, inhibit, or induce the same P450 isoenzymes may also contribute to reactions (25). Grapefruit juice inhibits intestinal (but not hepatic) cytochrome 3A4 and may increase serum levels of some drugs such as statins (26).

The reactive metabolites may induce adverse reactions by either directly causing cell injury, inducing apoptosis, or acting via an as yet undefined immune reaction. To date, there is no evidence that a specific antibody is involved in these reactions.

Typically, the treatment consists of stopping the drug. An HIV-positive patient who has had a rash and fever with sulfamethoxazole can usually be rechallenged without an adverse event. This success may be due to fluctuating differences in oxidative metabolism, or reductive capacity, at various stages of AIDS. With other drugs, rechallenge will usually result in repeat symptoms, occasionally severe. In most cases, these reactions are drug specific. Structurally similar drugs are often tolerated, e.g., loracarbef in patients who had a reaction to cefaclor (27).

### Prevention

The above discussion has focused on diagnosis and management of immune-mediated drug reactions, but the primary goal should be prevention. This means identifying the patient who is at risk of an immune reaction if given a particular drug. Unfortunately, the only reliable predictive test at present is an intracutaneous or intradermal skin test, and this is only standardized for penicillin and insulin. Skin testing for

other drugs is not standardized, in part because relevant antigens are not known and because many drugs induce nonspecific irritant reactions. Radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) tests (looking for specific IgE in serum) are less sensitive than skin testing, and in almost all cases the relevant drug antigens are not available for testing, generally because they are not known. *In vitro* or patch testing to detect other types of immune reactivity is either not predictive or not standardized.

One of the most common problems related to drug allergy concerns the patient with a history of reacting to a specific drug, who now ideally needs therapy with that drug or another in the same class. In this case, the first step is to get a detailed history of the original reaction. In some cases, it is obvious that the symptoms were not immune mediated; in some, there may be concern because of a family history of a reaction. A tendency to allergic disorders is inherited, but not a tendency to specific drug reactions, although this has recently been challenged (28). As noted above, there are very few definitive diagnostic tests to help clarify this situation. The goal is to identify the patient with sufficient IgE antibody who might be at risk of life-threatening anaphylaxis if given the drug. Almost all immune reactions that develop later in the course of drug administration are not life-threatening and can generally not be predicted. If the allergy cannot be defined adequately from history and available testing, there are three other possible approaches.

1. Use an alternate antibiotic, if possible. This is the safest approach.
2. Administer the drug initially via a "graded challenge," i.e., do cautious test dosing when there is a suspect history, but there is either no specific diagnostic test or no evidence of IgE antibody. Small incremental doses are given, under medical supervision. For example, give 1/100 of the therapeutic dose by the indicated route; if there is no reaction in one hour, proceed to 1/10 of the therapeutic dose. Likewise, if no reaction in one hour, proceed with the full dose. If there is a significant history or if the patient is medically unstable, one might elect to start with 1/1000 of the therapeutic dose. Once the first therapeutic dose is tolerated, anaphylaxis with subsequent doses given regularly is extremely unlikely.

3. "Desensitize" the patient if there is a history or testing suggestive of an IgE reaction to a drug and the patient currently needs that drug. The only absolute indication to do this is a patient with a positive skin test to penicillin who is pregnant and has syphilis. Very small incremental doses of the drug are administered IV or po every 20–30 minutes. The mechanism appears to be gradual absorption of specific IgE with incremental amounts of drug. Histamine release will probably occur gradually, but the sudden release of massive quantities is avoided. It is a potentially dangerous procedure and should be done in a monitored setting, by a physician capable of treating anaphylaxis. On average, it takes several hours.

### Penicillin Allergy

Many patients claim a history of penicillin allergy; however, when these patients undergo specific penicillin skin testing, only approximately 15% have positive skin tests indicating the presence of IgE in response to penicillin at the time of testing (29). The remainder have either lost the allergy over time or never had a true allergic reaction to penicillin; for example, some may have had viral exanthems. The reagents and techniques of penicillin skin testing are detailed by Bernstein et al. (30). The reagents should include the major determinant of penicillin (benzyl penicilloyl), commercially available as Pre Pen, and a mix of minor determinants which is not commercially available, or penicillin G as a substitute. Testing for serum levels of penicillin-specific IgE via a RAST or ELISA assay is available only for the major determinant and is not adequately sensitive to detect potential anaphylactic sensitivity.

A negative penicillin skin test means there is a 99% chance the patient will not have an IgE-mediated reaction to penicillin within 24 hours of administration (31). The 1% of patients who did react during clinical trials had minor symptoms, with no documented episodes of anaphylaxis. Because it is impossible to predict which patients will develop an immune reaction once they are exposed to the drug, this testing is not predictive of the chance of developing an IgE-mediated reaction occurring beyond 24 hours, or a T cell or other immune-mediated reactions, such as a morbilliform rash. However, with the possible exception of toxic epidermal

necrolysis, none of these later immune reactions are life-threatening.

Penicillin skin testing should be considered for any patient with a history of penicillin allergy who ideally needs a beta-lactam antibiotic for therapy. This should be done particularly when the alternate antibiotic is vancomycin. Generally, patients with a history of penicillin allergy are placed on vancomycin more commonly than are non-allergic patients (32). This practice is undoubtedly contributing to the problem of vancomycin-resistant microbial strains. If these patients are skin tested, approximately 85% would be able to tolerate a beta-lactam drug.

All penicillin derivatives should be considered antigenically cross-reactive. A history of allergy to penicillin and a negative penicillin skin test predicts that the patient is able to receive any "cillin" derivative (30). Rarely, patients may have isolated immune reactions to side chains of the aminopenicillins (ampicillin and amoxicillin). This sensitivity cannot be detected by penicillin skin testing, but may be detected by skin testing with the aminopenicillins (33). Approximately 5–10% of patients receiving aminopenicillins develop a morbilliform rash. This is discussed in detail in the section on morbilliform rashes. Patients with a history of such a rash should avoid further aminopenicillins, although, if necessary, most patients can tolerate later re-exposure without incident.

### Cephalosporin Allergy

Most physicians are not sure whether cephalosporins can be given to a patient with a history of penicillin allergy. The literature does not provide a definitive recommendation, since most reports are based only on history, without recording the results of specific skin testing. Penicillins and cephalosporins share the same beta-lactam ring structure. This ring is the site of metabolism, with production of antigenic determinants in the case of penicillin. This potential cross-reactivity, however, does not appear to be a significant clinical problem, as noted below. Table 2 details 468 patients with a history of allergy to penicillin and negative skin tests to penicillin; all but 3 (0.6%) tolerated subsequent cephalosporins (34, 35, personal communication). The three reactions were non-anaphylactic. Therefore, regardless of the history, if there is no evidence of an IgE response to penicillin by skin testing, such a patient should be able to tolerate a cephalosporin.

TABLE 2

*Patients with a History of Penicillin Allergy and Negative Skin Tests to Penicillin Challenged with Cephalosporins*

Reference	Patients Challenged	Reactions Within 24 Hours	Skin Test Reagents
Solley et al. (35)	151	2	Penicilloyl MDM*
Shepherd and Burton (34)	159	1 (itchy eye)	Penicilloyl Penicillin G
Shepherd (unpublished)	158	0	Penicilloyl Penicillin G
Total	468	3 (0.6%)	

\*MDM = minor determinant mix consisting of penicillin G and penicilloate

Even if patients have a positive skin test to penicillin, the overwhelming majority still tolerate a cephalosporin, as shown in Table 3. Since 1980, 160 such patients have been reported with three anaphylactic reactions (2%), only one of whom was in the U.S. (29, 34–39). Prior to 1980, the incidence was higher (40). This may reflect more early use of first-generation cephalosporins, some of which were contaminated with trace amounts of penicillin. There may have been cross-reactive IgE response to side chains; most patients received cephalothin or cephaloridine, both of which share a side chain that is similar to penicillin (40). Later cephalosporins have bulkier side chains. Potentially, these may stereochemically block IgE from binding to the beta-lactam ring. Patients can also make antibody to a side chain and not to the beta-lactam ring; as a result, they will only react to cephalosporins or penicillins with the same side chain (41). Based on the above, if a patient with a history of penicillin allergy is given a cephalosporin without further evaluation, the chance of a reaction is less than 1%. For example, for every 100 patients with a history of penicillin allergy, only approximately 15 will have positive skin tests. If the positive-skin-test patients are given a cephalosporin, fewer than 2% will react, i.e., fewer than one patient out of the original 100.

If patients have a history of allergy to penicillin and need a cephalosporin, they should undergo penicillin skin testing. If negative, they can receive a cephalosporin with less than a 1% chance of developing a non-life-threatening reaction (34, 35). If positive, they should either receive an alternate drug or undergo a cautious graded challenge with the cephalosporin under

medical supervision. The chance of anaphylaxis is less than 2%, but it is still possible.

### Monobactam and Carbapenem Allergy

The monobactam, aztreonam, does not seem to cross react with other beta-lactam drugs (41, 42). However, imipenem, a carbapenem, should be considered potentially cross-reactive with penicillin based on skin test data (43).

### Sulfonamide Allergy

IgE-mediated reactions to sulfa are uncommon, but diagnosis is hampered, as there is no standardized skin test reagent. The most common immune-mediated reaction is rash. Sulfa antimicrobials have been estimated to induce 70% of cases of drug-induced bullous rashes (11). Immune reactions to sulfonamides are thought to be directed to the sulfur atom attached to an aromatic amine. Drugs with this configuration, which potentially may be cross reactive, are listed in Table 4. They include all the sulfa antimicrobials and the cyclo-oxygenase 2 (COX II) inhibitor, celecoxib. The other COX II inhibitors do not have a sulfa tail. Although chemically distinct, dapsone has induced rash in 7% (44) to 20% (45) of HIV patients with a history of rash from sulfamethoxazole. The sulfonamide oral hypoglycemic drugs, thiazide diuretics and carbonic anhydrase inhibitors, have sulfa moieties; although there is very limited data, there is no evidence to date of immune reactions to these drugs in patients with a history of sulfa sensitivity. Because of the limited data, however, it may be prudent to use alternate treatment where possible, especially for any patient with a history of a bullous rash. This is an

**TABLE 3**  
*Patients with a History of Penicillin Allergy and Positive Skin Tests to Penicillin Challenged with Cephalosporins since 1980*

Reference	Patients Challenged	Reaction Within 24 Hours	Skin Test Reagent	Comments
Solley et al. (35)	27	0	Penicilloyl MDM*	
Rohr (36)	62	1	Penicilloyl MDM*	Mild urticaria / bronchospasm
Van Arsdell et al. (37)	6	0	Penicilloyl MDM*	
Blanca et al. (38)	19	2	Penicilloyl MDM*	Anaphylaxis to cefamandole
Shepherd (29)	3	0	Penicilloyl MDM*	
Shepherd and Burton (34)	9	0	Penicilloyl	
(Shepherd unpublished)	6	0	Penicillin G	
Macy (39)	28	0	Penicilloyl MDM*	
<b>TOTAL</b>	<b>160</b>	<b>3 (2%)</b>		

\*MDM = minor determinant mix

issue with acetazolamide, frequently prescribed for high-altitude symptom prophylaxis or treatment. Although there is no documentation of "cross reaction" with sulfa, patients are going to take acetazolamide in remote areas with limited access to medical care. It may be prudent to have these patients test dose the medication before leaving, although it can be argued that this could stimulate a later immune reaction.

HIV-positive patients who take trimethoprim-sulfamethoxazole prophylaxis for pneumocystis develop a morbilliform rash and fever 10–50 times more frequently than do non-HIV-infected patients (46). This is secondary to hepatic production of reactive metabolites of sulfamethoxazole, as discussed in the section on altered hepatic metabolism. In 95% of cases, patients can tolerate readministration (47). If the mechanism of the rash is T cell binding and killing of keratinocytes expressing MHC class II antigen plus bound drug, a possible pathogenesis is that viral infections increase interferon (INF) gamma, which increases MHC class II expression on keratinocytes and thus

leads to increased T cell binding (4). As CD4 counts decrease, the frequency of rashes also decreases (48). When the problem was first identified, multiple papers reported success readministering the sulfa drug slowly over weeks; subsequent publications reported success with progressively shorter protocols. The most recent protocol, with the highest success rate, gives the drug over six hours (47). This is a "graded challenge," not a "desensitization"; the only immune mechanism that can be manipulated in six hours is that of IgE antibody, and there is no evidence of IgE in these cases. If an HIV-positive patient has had a history of rash and fever with trimethoprim and sulfamethoxazole, it may be prudent to wait several weeks before rechallenge. The drug can then be given in incremental doses over several hours. It is also important to continue treatment if rash and fever recur (7). If there is any history suggestive of a bullous rash, readministration is contraindicated. Likewise, if the past reaction is other than rash and fever, for example, hepatitis or cytopenias, patients ideally should not be rechallenged.

**TABLE 4**  
*Sulfonamides and Other Derivatives*

Drugs	Brand Names
<b>Sulfonamide Antibiotics</b>	
sulfamethoxazole	Bactrim, Septra
sulfisoxazole	Pediazole
sulfamethizole	Urobiotic
sulfacetamide	Blephamide eye drops Sulfacet-R lotion
mafenide acetate	Sulfamylon cream
sulfanilamide	AVC cream or suppositories
sulfathiazole, sulfabenzamide, sulfacetamide	Sultrin triple cream
sulphasalazine	Azulfidine
<b>Non-steroidal Anti-inflammatory</b>	
celecoxib	Celebrex
<b>*Carbonic Anhydrase Inhibitors</b>	
acetazolamide	Diamox
dichlorphenamide	Daranide
dorzolamide, brinzolamide	Trusopt, Cosopt, Azopt
<b>*Sulfonylurea Oral Hypoglycemics</b>	
glyburide	DiaBeta
glipizide	Glucotrol
chlorpropramide	Diabenase
tolazamide	
<b>*Diuretics</b>	
thiazides	HydroDIURIL, Diuril, Enduron, Microzide
others	Furosemide

\*Although these drugs contain sulfa in their chemical structure, there are no reports of patients with a history of sulfa antibiotic sensitivity subsequently reacting to one of these.

### Allergy to Quinolone Antibiotics

Quinolone antibiotics induce nonspecific histamine release; for example, an intradermal injection of as little as 0.02 mL of a 0.0001 mL concentration will commonly induce a hive. For this reason, specific skin testing generally cannot be done. Additionally, there are no *in-vitro* assays for specific IgE responses to quinolones. There are several reports of anaphylactic reactions with ciprofloxacin, many with first known exposure, which strongly suggests non-immune-mediated histamine release (49). HIV-positive patients may be at greater risk of reactions (49). The author is aware of several cases where such patients subsequently had a comparable reaction to another quinolone. For these reasons, if a patient has a history compatible with anaphylaxis or significant urticaria from one quinolone, until further

diagnostic testing is available, that patient should avoid all quinolones.

If the history of adverse reaction is a morbilliform rash, it is unclear whether the patient can be rechallenged. This is a less common situation. In all of these cases, an alternate drug should be given, if possible. If a quinolone must be administered in this case, the patient should undergo a graded challenge, as described above. There is one report of a successful “desensitization” to ciprofloxacin in a patient who had had a prior reaction (50).

### Allergy to Muscle Relaxants

Allergic reactions often result from muscle-relaxant drugs administered during anesthesia (51), particularly from suxamethonium, gallamine, vecuronium, and pancuronium (52). Most are presumed to be mediated by specific IgE antibody, although only a small percent of patients with a positive skin test develop symptoms with exposure (53). This category of drugs may also be capable of non-antibody-mediated activation of basophils, with resultant release of histamine.

### Allergy to Local Anesthetics

Despite the perception that many patients are allergic to local anesthetics, true IgE-mediated reactions are extremely rare; there is disagreement as to whether any well-documented case has been reported (54). Reported reactions are most likely due to other reasons, including hyperventilation, vasovagal reactions, numbness of the pharynx from extravasated anesthetic, or inadvertent intravascular injection of epinephrine (added to most local anesthetics to vasoconstrict the area). Regardless of the history, the easiest approach is to pick an alternate anesthetic, as listed in Table 5. The patient should undergo skin prick and intradermal skin tests with the alternate, using incremental doses, depending on the history, followed by a subcutaneous challenge with approximately 0.2 mL. (Dental vials have 1.8 mL.) If no reaction ensues, the patient will not react significantly when given ten times the dose. Ideally, testing should be done with local anesthetics without epinephrine, as skin blanching may occur, which can be misinterpreted as an immune reaction. Then a note needs to be written documenting that the patient has successfully tolerated the local anesthetic. Although there is almost no concern regarding an IgE-mediated reaction, the

**TABLE 5**  
*Common Local Anesthetics*

Generic Name (Brand Name)
procaine (Novocain)
bupivacaine (Marcaine, Sensorcaine)
lidocaine (Xylocaine)
mepivacaine (Carbocaine, Polocaine)
prilocaine (Citanest)
benzocaine — in topical preparations and some sore throat lozenges
pramoxine — in topical preparations
proparacaine — (Alcaine, Ophthalmic) eye drops

above needs to be done to reassure the patient and the referring dentist or physician.

### **Anaphylactoid or Non-immune-Mediated Drug Reactions**

A variety of drugs cause reactions that are clinically indistinguishable from true allergic reactions. In these cases, however, the specific immune system is not involved. The reactions are partly related to the dose and rate of infusion. In contrast to true IgE-mediated reactions, life-threatening reactions with minuscule amounts of drug are very unlikely. For this reason, many of these drugs can be readministered after pretreatment and appropriate dosing. Vancomycin, protamine and opioids induce symptoms by non-immune-mediated histamine release, aspirin and non-steroidal anti-inflammatory drugs via enzyme blockade. Although not technically a drug, radiocontrast media is included here as it also induces nonspecific histamine release in sensitive individuals.

#### **Vancomycin**

Administration of vancomycin is commonly associated with “the red man syndrome” characterized by flushing, erythema, and pruritus, characteristically in the upper extremities and torso. Hypotension can occur. These symptoms appear to be due to nonspecific histamine release associated with rapid infusions. If the drug is given again to adults with an infusion rate of one gram over two hours (instead of the usual one hour), most patients tolerate readministration (55). Rarely, the infusion needs to be slower. Patients may also be helped by pretreatment with an antihistamine.

Vancomycin is also associated with morbilliform rashes. These are more common with prolonged courses and probably are immune

mediated. Management is discussed in the section on morbilliform rashes.

#### **Protamine**

Protamine is commonly used to reverse heparin anticoagulation during cardiac and other procedures. As with vancomycin, IV infusion can trigger non-immune-mediated histamine release, with resultant symptoms of anaphylaxis (56). Reactions to protamine, however, are up to 25 times more frequent in diabetic patients taking NPH (neutral protamine Hagedorn) insulin (57). It is unclear whether this is immune mediated, but it is of concern, as diabetic patients frequently require cardiac procedures. At present there is no accepted substitute. Several reference laboratories can detect IgE or IgG specific for protamine. If the results are positive, a patient is at increased risk of anaphylaxis. It is unclear whether pretreatment with antihistamine and possibly steroids is protective. In all cases where an NPH-dependent diabetic patient requires protamine, it should be given as slowly as possible, with close monitoring of vital signs.

#### **Opioids / Narcotic Pain Medications**

Morphine, meperidine and codeine are non-specific histamine liberators. They bind to a specific receptor on mast cells, with resultant histamine release and the clinical presentation of pruritus and urticaria. More severe reactions are very unusual. The effect is somewhat dose dependent and is perhaps associated with the potency of the drug. If a patient has severe symptoms, ideally a non-opioid pain medication should be given, such as ketorolac tromethamine (Toradol®), but no one should be denied narcotic analgesics because of concern about anaphylaxis. Patients with this history should undergo a graded challenge. Most will tolerate smaller doses, and many are helped by coincident antihistamines.

#### **Aspirin and Non-steroidal Anti-inflammatory Drugs**

These drugs are associated with aspirin-sensitive respiratory disease, a triad of rhinosinusitis, nasal polyps and asthma (58). Approximately 30–40% of adults with asthma and rhinosinusitis are sensitive to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) (59). If exposed, they develop symptoms rang-

ing from increased nasal congestion to severe asthma and anaphylaxis. Rarely, patients have anaphylactic sensitivity to aspirin and NSAIDs without the triad symptoms. The mechanism may be blockade of the cyclo-oxygenase enzyme with resultant overproduction of leukotrienes, especially LT<sub>3</sub>, 4 and 5. These are potent bronchoconstrictors. This sensitivity appears to be related only to blocking the COX I isoform of the enzyme, as patients with aspirin-induced asthma have been shown to tolerate COX II inhibitors (60). Why only a subset of patients have this sensitivity to aspirin and NSAIDs is not known. Unfortunately, it is a class effect, but some drugs induce more severe symptoms. This appears to be related to the strength of the enzyme blockade. Patients may tolerate weaker COX I inhibitors, such as acetaminophen or salsalate, but usually these do not provide adequate symptom relief.

There is no specific diagnostic test to identify sensitive patients, or to determine which, if any, NSAIDs a patient may tolerate. At present, this can only be done by a very cautious graded challenge, following pulmonary spirometry, by a physician with experience in the treatment of anaphylaxis. In many cases, patients will tolerate low doses, but develop asthma with higher concentrations. In select cases, it is possible to “desensitize” patients with severe triad symptoms to aspirin and maintain them on a regular daily dose. This has been associated with clinical improvement in these patients (61). One study documented successful oral challenge-desensitization over several hours in 11 patients with aspirin- or NSAID-induced angioedema and urticaria (62). Leukotriene inhibitors blocking lipooxygenase activating factor or LT<sub>4</sub> receptors have also helped some of these patients, but have not been shown, so far, to block specific aspirin or NSAID sensitivity.

### Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are associated with a cough in up to 25% and angioedema in 0.1–0.2% of treated patients (63). The precise mechanism is not known, but is likely to be related to alterations in kinin generation in sensitive patients. ACE inhibitors block an enzyme responsible for kinin metabolism. There is no evidence of specific immune mediation. The angioedema can be potentially life threatening; therefore, any patient with angioedema should be checked to see if he or she is taking an ACE inhibitor. The

onset of angioedema reactions is variable, but usually occurs after one month or more of treatment (63).

### Radiocontrast Media

Histamine-mediated reactions to radiocontrast media are common. There is no evidence of specific immune mediation. Reactions appear to be related to intravascular injections of hyperosmolar material. The specific mechanism is not known; possible mechanisms include activation of blood basophils or complement with production of the fifth component of complement (C5a), which is capable of directly releasing histamine from mast cells via a specific complement receptor (64). Patients who react appear to have more reactive vascular endothelium. Reactions seem to occur only with intravascular administration. Newer “non-ionic / low-osmolar” preparations are associated with a lower incidence of reactions, but the frequency of severe reactions is similar to that with hyperosmolar agents (65). Repeat reaction can be prevented by pretreatment with steroids and antihistamines, as noted in Table 6 (66). Patients at risk of a reaction to radiocontrast media should be off beta-blockers (67) and possibly inhibitors of angiotensin II (2) before the procedure. Recent reports suggest that, rarely, some patients may develop delayed rashes (68).

### Reactions to Excipients in Drugs

All drugs have multiple excipients added. These may include preservatives and coloring agents. For example, a 1.25-mg tablet of Premarin® (conjugated estrogens) has 16 excipients in addition to estrogen. Allergic reactions to the additives are very unusual, but may possibly occur to propylene glycol, parabens, and thimerosal. If this is suspected, the patient should be tested with different drugs containing

**TABLE 6**  
*Pretreatment Regimen to Block Repeat Reactions to Radiocontrast Media*

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prednisone 50 mg po: 13, 7 and 1 hour before the procedure.
diphenhydramine 50 mg IV or IM: one hour before the procedure.
Patients at risk should ideally be off beta-blockers and angiotensin II receptor antagonists at the time of the procedure.

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Adapted from Reference 66.

the same additives. IgE-mediated reactions have been described with gelatin, used as a stabilizer in some vaccines for measles, mumps and rubella (MMR), diphtheria, pertussis, and tetanus (DPT) and varicella, as well as for some preparations of erythropoietin. With one exception, all reported cases are from Japan (69).

### Multiple Drug Allergy

It has been reported that 18–27% of patients who react to one drug, especially an antimicrobial, have an increased frequency of similar subsequent reactions to chemically distinct drugs (70). A more recent study, however, found no difference in reactions to non-beta-lactam antibiotics between patients with documented allergy to penicillin and those with no evidence of prior immunologic drug reactions (71). In all cases where patients report adverse reactions to multiple drugs, a careful history will usually limit the possible offending drugs. Many patients mistakenly believe that an increased sensitivity to known side effects is caused by allergy. In some cases specific skin testing may help to differentiate these responses. If questions remain and the patient needs a specific drug, a graded challenge or desensitization can be done.

### Summary

Hypersensitivity reactions to drugs may not be readily apparent. The key is to suspect this diagnosis in any patient with unanticipated signs or symptoms within several weeks of starting a new medication. With the notable exceptions of anaphylaxis and severe blistering exfoliative rashes, most immune-mediated reactions to drugs are not life-threatening and generally resolve once the drug is discontinued.

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