Background
An estimated 3% of patients develop allergic reactions to sulfonamide antibiotics. The most common type of reaction is a maculopapular rash. Rarely, patients develop life-threatening reactions like anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrosis. For many years, there has been debate in the medical community whether all sulfa drugs should be avoided in patients allergic to sulfonamide antibiotics. This document discusses the different classifications of sulfonamide drugs and the risks for cross-reactivity. A chart listing sulfonamide drugs by their chemical subclass is also included.

How are Sulfa Drugs Classified?
A sulfonamide is any compound that contains a SO₂NH₂ moiety. Sulfonamides are divided into three different groups based on chemical structure. The first group, the sulfonylarylamines, have a sulfonamide moiety directly attached to a benzene ring with an unsubstituted amine (-NH₂) moiety at the N4 position. This group consists primarily of the sulfonamide-type antibiotics as well as three protease inhibitors (amprenavir [Agenerase], darunavir [Prezista], and fosamprenavir [Lexiva]). The second group, the nonsulfonylarylamines, also have a sulfonamide moiety attached to a benzene ring or other cyclic structure, but they do not have an amine group at the N4 position. The third group, known as the sulfonamide moiety-containing drugs, have a sulfonamide group that is not connected to a benzene ring like in the other groups. The specific agents included in these three groups are summarized in the attached table.

The Cross-Reactivity Controversy
Several case reports suggest patients that are allergic to sulfonamides from one group (e.g., sulfonylarylamines) may be at increased risk for developing an allergic reaction to a sulfonamide from another group. This is known as cross-reactivity. However, there is no data from well designed trials that show that sulfonamides from different groups cross-react. An alternative theory to sulfonamide cross-reactivity is that patients allergic to one drug may be at higher risk for being allergic to other, even structurally unrelated, drugs.

This hypothesis was tested in a retrospective cohort study by Strom et al (n=20,226) that evaluated the incidence of allergic reactions following initiation of sulfonamide nonantibiotic drugs. Patients that had previously experienced an allergic reaction to a sulfonamide antibiotic had a higher occurrence of allergic reactions than did patients with no history of hypersensitivity to sulfonamide antibiotics (9.9% versus 1.6%, adjusted odds ratio 2.8; 95% confidence interval, 2.1 to 3.7). However, patients with a prior sulfa allergy were even more likely to have an allergic reaction to penicillin, obviously a structurally unrelated drug, than they were to a sulfonamide nonantibiotic. Additionally, the risk of an allergic reaction after receiving a sulfonamide nonantibiotic was HIGHER in patients with a history of penicillin allergy than in those with a history of hypersensitivity to sulfonamide antibiotics.

Some experts also argue that cross-reactivity isn’t possible between the sulfonylarylamines and the other types of sulfonamides because of structural differences. The one structural similarity found among the three groups, the SO₂NH₂ moiety, hasn’t been shown to interact with the immune system. However, there are at least two known types of allergic reactions related to the sulfonylarylamine structure that require functional groups NOT present in the nonsulfonylarylamines or sulfonamide moieties.

The first, type 1 immunological reaction, requires the presence of a heterocyclic ring at the sulfonamide-N1 position. This reaction is immunoglobulin (Ig) E mediated, presents usually within one to three days after initiation of medication, and is commonly associated with a maculopapular eruption or an urticarial rash.
More serious reactions including angioedema, hypotension, and anaphylaxis may also occur, especially with repeat exposure.2,7 The second, more common hypersensitivity reaction, requires the presence of an unsubstituted amine group at the N4 position.2,7,8 Cytochrome P-450 oxidation of the N4 arylamine results in the formation of cytotoxic or immunogenic hydroxylamine and nitrosamine metabolites.7,8 This reaction usually develops seven to 14 days after initiation of drug therapy and resolves upon discontinuation of medication.2 Presentation consists of a fever and a nonurticarial rash that may progress to erythema multiforme and multi-organ toxicity.

The difference in chemical structure between the sulfonarylaminest and other types of sulfonamides implies that cross-reactivity is unlikely. However, T-cell mediated immune response to the unmetabolized, nonhaptenated parent sulfonamide antibiotic has been reported to occur occasionally.7 It is unknown whether T-cell recognition is related to the sulfonamide moiety or some other functional group. Until the mechanism behind T-cell recognition is more clearly understood, cross-reactivity between sulfonarylaminest and the other types of sulfonamides remains theoretically possible.

The protease-inhibitors amprenavir and fosamprenavir are sulfonamides with an N4 arylamine, like the sulfonarylamine antibiotics. The product labeling for these agents state that the potential for cross-sensitivity with other sulfonamides is unknown, but they should be used with caution in people with sulfonamide allergy.3-5 In initial clinical trials, 16 patients with a history of sulfonamide allergy were prescribed amprenavir.2 Five (31%) of these patients developed a rash which resulted in discontinuation of amprenavir in two patients. In a clinical study with fosamprenavir used as the only protease inhibitor, rash occurred in 20% of patients with a history of sulfonamide allergy compared to 33% of patients with no history of sulfonamide allergy.4

Other drugs (e.g., some local anesthetics, dapsone, and procainamide) do not contain a sulfonamide moiety; but, like the sulfonarylaminest, contain an N4 arylamine.7 The same is true for sunscreens that contain para- amino-benzoic acid (PABA) derivatives.1 Although the significance of this structural similarity is unknown, there have been reports of cross-sensitivity between sulfonamides and dapsone, a sulfone.1,9

Cross-reactivity between dapsone and sulfonarylaminest appears to be especially prevalent in human immunodeficiency virus (HIV) infected individuals, who are already at a much higher risk of allergic reaction to sulfonamides.1,9 The package labeling of dapsone does not address the issue of cross-sensitivity with sulfonamides. However, experts state that dapsone may be considered in HIV-infected patients with mild hypersensitivity reactions to trimethoprim-sulfamethoxazole (Bactrim, Septra).9

Agents containing sulfur, sulfites, sulfates, and saccharin often confuse clinicians about their potential for cross-reactivity with sulfonamides. Medications that contain sulfur such as amoxicillin (Amoxil), captopril (Capoten), omeprazole (Prilosec), ranitidine (Zantac), spironolactone (Aldactone), and sulindac (Clinoril) are not sulfonamides and do not cross-react.1 Sulfites (sulfur dioxide, sodium sulfite, sodium bisulfite, potassium bisulfite, sodium metabisulfite, and potassium metabisulfite) are used in foods and drugs (e.g., EpiPen, Pred Forte, Garamycin injectable, etc) as antioxidants.1,10 They are also chemically unrelated to sulfonamides and there is no risk of cross-sensitivity. However, sulfites may cause their own reactions such as dyspnea, wheeziness, and chest tightness in patients with asthma.10 Sulfates (e.g., zinc sulfate, morphine sulfate, etc) are also not chemically related to sulfonamides. Saccharin is an O-toluene sulfonamide derivative. This artificial sweetener is an ingredient in many liquids and tablets, but is not required to appear in drug labeling.1,10 Dermatologic reactions and cross-reactivity with sulfonamide antibiotics have been reported. The American Academy of Pediatrics recommends that children with sulfonamide allergy avoid saccharin [Evidence level C, Consensus].10

**Commentary**

The majority of available evidence suggests that nonsulfonarylamine and sulfonamide moiety-containing drugs need not be routinely avoided in patients with a history of allergy to sulfonarylaminest.2,6,7 Although the nonsulfonarylaminest and sulfonamide moieties are not chemically related to sulfonamides, there have been reports of cross-sensitivity between the two.1,9-11

More...
may cause allergic reactions themselves, because of the stereospecificity of the reaction associated with sulfonylarylalmines, cross-reactivity is unlikely. The question that remains unanswered is the mechanism behind T-cell recognition, and whether it is related to the sulfonamide functional group.7

Unfortunately, the product labeling of many nonantibiotic sulfonamide agents does not correlate with what is known scientifically. For instance, many diuretics are either contraindicated or contain warnings regarding their use in patients with a history of sulfonamide allergy (see table).1,2 The inconsistency between product labeling and available evidence is likely because some of these agents (e.g., hydrochlorothiazide) were marketed many years before these newer theories refuting cross-reactivity were developed.

The inconsistency between product labeling and scientific evidence places clinicians in a difficult position. The routine avoidance of sulfonamide-containing drugs in patients with a history of sulfonamide allergy can unnecessarily complicate or compromise patient care. However, to ignore the product labeling recommendations places clinicians at risk of liability.

Patient-specific factors should be considered when evaluating the risk of an allergic reaction.1 Allergic reactions may be less common in infants and the elderly, in theory because the immune system is immature or senescent. Factors that may predict drug allergy include a family or personal history of drug allergy, some concurrent illnesses (e.g., HIV), and slow acetylator phenotype.3 One theory called the “danger hypothesis” suggests that co-stimulatory signals such as genetic predisposition and environmental stress (e.g., infection) cause the immune system to become activated resulting in an immune response to otherwise well-tolerated drugs.8

Ultimately, clinicians will need to make the decision of whether to initiate sulfonamide drugs in sulfonamide allergic patients on a case-by-case basis. Some experts support using nonsulfonylarylamine and/or sulfonamide moiety-containing medications in patients allergic to sulfonylarylalmines if alternative therapy with structurally unrelated compounds is not possible [Evidence level C; expert opinion].2 Exceptions include patients with serious allergic reactions and/or multiple medication allergies.2 In some situations, sulfonamide desensitization may be necessary.


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Levels of Evidence
In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)</td>
</tr>
<tr>
<td>B</td>
<td>Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study</td>
</tr>
<tr>
<td>C</td>
<td>Consensus Expert opinion</td>
</tr>
<tr>
<td>D</td>
<td>Anecdotal evidence In vitro or animal study</td>
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Project Leaders in preparation of this Detail-Document: Sherri K. Boehringer, Pharm.D., BCPS (Original 2005), Stacy A. Hester, R.Ph., BCPS, Assistant Editor (May 2010 update)

References

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Allergic Cross-reactivity Among Beta-lactam Antibiotics: An Update

Introduction
Beta-lactams are first-line treatments for a number of common infections. Patients allergic to penicillins are often treated as also being allergic to cephalosporins. Historical data have suggested that up to 10% of patients allergic to penicillins are also allergic to cephalosporins. In addition, cross-reactivity with penicillins and carbapenems has been cited at nearly 50%, with little scientific data to back up the claim. It’s easy to see why penicillin-allergic patients might be prescribed a second-line therapy that is less effective, more expensive, more toxic, or has a broader spectrum of activity than necessary. More recent data suggest that the true incidence of allergic cross-reactivity between the penicillins and other beta-lactam antibiotics is much lower than originally reported. This is important for a number of reasons, including the fact that some non-beta-lactam alternative therapies, such as macrolides for otitis media, are no longer preferred options due to high bacterial resistance rates. This document reviews the types of penicillin allergies, assesses current data on true cross-reactivity between penicillins and other beta-lactams, and provides treatment considerations.

Types of Penicillin Allergies
Approximately 10% of the population will report a history of an allergy to penicillin. However, up to 90% of these individuals will be able to tolerate treatment with a penicillin and further, will not have a positive skin test. The designation of “penicillin allergy” is not necessary for these individuals.

Several types of allergic reactions to penicillins are described in the medical literature. One method of classifying penicillin allergies is as follows:
- immediate/accelerated (type I reactions);
- late (type II, III, and IV reactions);
- other (idiopathic reactions).

Immediate/accelerated reactions typically occur within one hour (immediate) or one to 72 hours (accelerated) after administration of a penicillin. These reactions are mediated by penicillin-specific IgE antibodies. Clinical signs of an immediate or accelerated reaction include anaphylaxis, a drop in blood pressure, swelling of the larynx, wheezing, angioedema, and hives or an itchy rash.

Late reactions tend to occur more than 72 hours after exposure to a penicillin. As previously mentioned, these are sometimes referred to as type II, III, and IV reactions. Type II reactions are mediated by IgG antibodies and complement. Clinical signs include increased red blood cell and platelet clearance by the lymphoreticular system. Type III reactions are mediated by IgG and IgM immune complexes. Clinical signs include serum sickness and tissue injury. Type IV reactions are mediated through an unknown mechanism. A clinical sign is contact dermatitis.

Idiopathic reactions also tend to occur after 72 hours of exposure to a penicillin. Idiopathic reactions are mediated through unknown mechanisms. Clinical signs include a maculopapular or morbilliform rash which can progress to Stevens-Johnson syndrome.

An example of an idiopathic reaction is the rash that can occur following administration of drugs such as ampicillin and amoxicillin in patients with an Epstein-Barr virus (EBV) infection. The risk appears to be highest in patients who receive ampicillin. This rash typically occurs seven to 14 days after beginning antibiotic therapy. It is described as a red, itchy, maculopapular rash, involving primarily the upper extremities and trunk. The rash can be accompanied by fever, swelling of the lips and eyelids, diarrhea, and joint pain. Patients who develop this rash are likely to be able to tolerate penicillins in the future.

More...
**Diagnosis of a Penicillin Allergy**

Prior to treating a patient who reports a penicillin allergy, a thorough history of the patient’s allergy should be obtained. Examples of questions the patient should be asked include the following:3,8

- How old were you when the reaction occurred?
- Please describe the reaction.
- When did the reaction occur? After the first dose? After the tenth dose?
- How was the penicillin administered? Orally? Intravenously?
- Were you taking any other medications at the same time?
- When the penicillin was stopped, what happened?
- Have you since taken a penicillin, cephalosporin, carbapenem, or monobactam?

Only immediate or accelerated penicillin allergies (IgE-mediated) can be diagnosed with penicillin skin testing. Results from studies suggest that just 10% to 20% of patients who report a penicillin allergy will have a positive penicillin skin test.8,11 However, patients with a negative penicillin skin test can still be allergic to penicillins. In most of these cases, the allergy is a late or idiopathic type reaction.

Skin testing is the **best method** for diagnosing an IgE-mediated penicillin allergy. Skin testing is usually performed by an allergist. It typically involves placement of positive (histamine) and negative (saline) controls, and then an epidermal or intracutaneous prick test. If the penicillin prick test is negative, an intradermal skin test is done. Anaphylaxis can occur with skin testing. Therefore, providers performing penicillin skin testing must be prepared to quickly treat patients who have anaphylactic reactions. Other tests, such as patch testing, radioallergosorbent tests, and enzyme-linked immunoassay, are less reliable.3

Current recommendations for penicillin skin testing are to administer both the major determinant (benzylenpicilloyl-polyslyine [Pre-Pen]) of penicillin allergy, and the minor determinant (e.g., penicillin G).3,7 The terms major and minor determinant refer to the amount of drug that is metabolized to that component.12 Allergic reactions are linked to the minor determinant in a large majority of cases.11

Unfortunately, minor determinant skin testing is not standardized and can vary from place to place.

**Cephalosporin Cross-reactivity**

Studies performed in the 1960s and 1970s suggested that the rate of cross-reactivity between penicillins and cephalosporins was as high as 50%.13 However, early cephalosporins may have been contaminated with trace amounts of penicillins,6 and the rate of cross-reactivity has traditionally been cited as 8% to 10%. Note that people with a penicillin allergy, compared to those without a penicillin allergy, are three times more likely to have an adverse effect to an unrelated drug.4

Current data suggest that the rate of cross-reactivity between penicillins and cephalosporins is probably less than 1% (approximately 0.1% of patients without skin test-confirmed penicillin allergy, 0.1% for those with mild reactions to penicillin, and 2% for patients who are penicillin skin test positive). This cross-reactivity is likely determined by the sharing of identical R-group side chains and not the beta-lactam structure itself.3,4,8

In general, the rate of allergic cross-reactivity is highest between penicillins and first-generation cephalosporins. The risk for cross-reactivity may reach almost 40% between penicillins and cephalosporins with identical R-group side chains.6 Penicillins and cephalosporins with which have the same R-group side chains include the following:3,6

- amoxicillin, cefadroxil, cefprozil
- ampicillin, cefaclor, cephalaxin

**Carbapenem and Monobactam Cross-reactivity**

Cross-reactivity between penicillins and carbapenems (i.e., imipenem, meropenem, ertapenem, or doripenem) has been reported. In early studies, the cross reactivity of penicillin and imipenem was cited at 47%,14 but more recent studies estimate the likelihood of cross-reactivity to be close to 1%.15 The large difference in reaction rates is thought to be because of a small patient population and methods of taking allergy histories in the early studies.12

Meropenem cross-reactivity is estimated at 0.9% in studies, although conservative statistical estimates cite a rate of 5.2% or less.16,17

More . . .
There are no studies of ertapenem or doripenem cross-reactivity in patients with a penicillin allergy.

Cross-reactivity between penicillins and aztreonam, a monobactam, does not generally occur. However, aztreonam and ceftazidime have the same R-group side chain. Therefore the potential for cross-reactivity to aztreonam exists in patients allergic specifically to ceftazidime. In addition, aztreonam should be used cautiously in cystic fibrosis patients reporting hypersensitivities to beta-lactam antibiotics.

**Treatment Recommendations**

Ideally, all patients who report symptoms consistent with an IgE-mediated reaction to penicillins would be evaluated by an allergist or immunologist. This could help reduce the unnecessary use of more broad-spectrum antibiotics. In the absence of skin testing, the risks and benefits of different treatment options must be weighed.

In general, patients who report symptoms consistent with an immediate or accelerated reaction (type I) to penicillin (or are skin test positive to penicillin) should not receive any penicillin, unless they undergo desensitization (also called induction of drug tolerance). Usually desensitization is a last resort if a penicillin is the treatment of choice for an infection and no acceptable nonpenicillin alternatives are available. Desensitization involves incremental doses of an oral penicillin every 15 minutes for a total of nearly four hours before a full dose (oral or IV) is given. An example of a penicillin desensitization protocol is available in *Morbidity and Mortality Weekly Report* found at [http://www.cdc.gov/std/treatment/2006/penicillin-allergy.htm#skintesting](http://www.cdc.gov/std/treatment/2006/penicillin-allergy.htm#skintesting).

Individuals with vague or distant histories of penicillin allergy may be candidates for receiving penicillins via graded challenge, although it is important to note that up to one-third of these individuals will have a positive skin test. (Graded challenge does not modify an individual's immune response, it is simply a more cautious way of administering the drug.) Penicillin allergies are likely to wane over time. For example, about 80% of patients who report symptoms of an IgE-mediated allergic reaction to a penicillin ten years ago will not presently have a positive skin test.

Those who report immediate or accelerated reactions to semisynthetic penicillins such as amoxicillin or ampicillin may be able to tolerate other penicillins. Skin testing with penicillin may be helpful to determine this.

Historically, data suggested that patients who reported an immediate or accelerated reaction to a penicillin (or are skin test positive to penicillin) should not receive a cephalosporin. However with certain precautions (see below), some second, third, and fourth generation agents may be able to be safely administered to patients with an immediate or accelerated reaction to a penicillin. (The manufacturer of the fifth generation cephalosporin, ceftaroline, advises caution in beta-lactam allergic patients until more data are available on the potential for cross-reactivity.)

Since side chain similarity appears to be important in allergic cross-reactivity between the penicillins and cephalosporins, those with an immediate or accelerated reaction to amoxicillin should not receive cefadroxil or cefprozil without desensitization and those with an immediate or accelerated reaction to ampicillin should not receive cefaclor or cephalaxin without desensitization.

Administration of a cephalosporin to a patient who reports an immediate or accelerated penicillin allergy (or is skin test positive to penicillin) should be done cautiously. There is not good evidence that cephalosporin skin testing will predict IgE-mediated reactions to cephalosporins. Providers may opt for rapid desensitization to the cephalosporin, or for a graded challenge. For graded challenge with oral cephalosporins, 10% of the first dose is administered, followed one hour later by the full dose, under observation, in the absence of a reaction. For graded challenge with intravenous cephalosporins, 1% of the full dose is administered, then 10% of the full dose, then the full dose, separated by one hour each, under observation, in the absence of a reaction.

Cephampenems can be used in patients who report an immediate or accelerated type reaction with a penicillin (or are skin test positive to penicillin), after optional skin testing and a graded challenge.

For example, if a patient needs to be skin tested with imipenem, a concentration of 0.5 mg/mL of imipenem-cilastatin should be used.
If the skin test is negative, some studies have used a graded challenge: 1% of the dose in the first hour, 10% of the dose in the second hour, and a full imipenem-cilastatin dose in the third hour if no reaction has occurred.15

Skin testing for meropenem should be performed with a concentration of 1 mg/mL. Then, one of two equally safe graded challenge regimens can be chosen: 1% of the dose in the first hour, then 10% of the dose in the second hour, and the full dose in the third hour if no reaction occurs in the first or second hour; or 10% of the dose in the first hour, and the full dose in the second hour if no reaction occurs in the first hour.16

In some cases, it may be preferable to use an antibiotic from a different drug class (a non beta-lactam) for patients with penicillin allergy. However, the latest treatment guidelines for infections such as sinusitis and acute otitis media recommend against the routine use of some alternatives such as macrolides due to an increase in resistance. For more information, see our PL Detail-Document, Should Macrolides Be Used for Respiratory Tract Infections?

Treatments for patients reporting a cephalosporin allergy may also be chosen based on R-group side-chain similarities. Patients with an immediate or accelerated allergy to a cephalosporin should not receive a cephalosporin with the same R-group side chain without desensitization to that drug.3 For example, a patient with an IgE-mediated reaction to cefuroxime should not receive cefoxitin.3 Likewise, a patient with an IgE-mediated reaction to ceftriaxone should not receive cefotaxime or cefpodoxime.3 A cephalosporin with a different side chain may be able to be used safely. However, consideration should be given to the use of either rapid desensitization or graded challenge, depending on the severity of the reaction.3,4

Patients who report an immediate or accelerated allergy to ceftazidime should not receive aztreonam, since these drugs have identical R-group side chains.3 As previously mentioned, aztreonam should be used cautiously in cystic fibrosis patients reporting hypersensitivities to beta-lactam antibiotics.12,19

If a patient has a documented immediate or accelerated reaction to a carbapenem, use of another agent from that particular class should be avoided until more data are available.

**Conclusion**

The incidence of allergic cross-reactivity among beta-lactam antibiotics appears to be less than historically thought. Ideally, all patients who report symptoms consistent with an IgE-mediated reaction to penicillins would be evaluated by an allergist or immunologist. This could help reduce the unnecessary use of more broad spectrum antibiotics.3,4,6,7

A patient’s allergy history should be carefully obtained and the decision about which antibiotic class to administer should be based on this information. Under certain conditions, patients with an IgE-mediated penicillin allergy may be able to safely receive a cephalosporin, particularly second, third, and fourth generation cephalosporins.3

The carbapenems and aztreonam pose little risk to patients with a true type I penicillin allergy in most cases, although skin testing and graded challenge is recommended prior to treatment with carbapenems.3

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**Project Leader in preparation of this PL Detail-Document:** Stacy A. Hester, R.Ph., BCPS, Assistant Editor

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Sulfa Drugs and the Sulfa-allergic Patient

Healthcare providers often have questions about whether or not certain drugs can be used in a patient with a sulfa allergy. There are three different classifications of sulfa drugs, or sulfonamides, based on chemical structure: sulfonylarylamines (includes sulfa antibiotics), nonsulfonylarylamines, and sulfonamide moiety-containing drugs. About 3% of individuals have an allergy to the sulfa antibiotics, such as sulfamethoxazole. Most commonly, this manifests as a maculopapular rash. Generally, nonsulfonylarylamines and sulfonamide moiety-containing drugs need not be avoided in people with allergies to sulfa antibiotics. Available evidence suggests that cross-sensitivity (also called cross-reactivity) is unlikely between the three different sulfa chemical classes. However, individuals with allergic reactions to sulfonylarylamine antibiotics may be more likely to experience allergic reactions to the other types of sulfonamides. This is probably because these patients have a predisposition for allergies instead of cross-sensitivity with sulfonylarylamine antibiotics. It should be noted that sulfates, sulfur, and sulfites are chemically unrelated to sulfonamides and do not cross-react. It’s important to note that package labeling doesn’t always match up with available evidence regarding cross-sensitivity of these drugs. It’s a good idea to investigate the patient’s drug allergy history and check the evidence for cross-sensitivity before ruling out a needed therapy. The following chart lists sulfa drugs according to classification based on chemical structure. Information from the product labeling regarding administration to patients with sulfa drug allergy and additional clinical evidence is also included.

### Sulfonamide-Containing Agents: Summary of Cross-Sensitivity Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Product Labeling Recommendations in Sulfonamide Allergy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylarylamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Contraindicated</td>
<td>Contraindications include ophthalmic (sodium sulfacetamide), topical (silver sulfadiazine [SSD, Silvadene]), and vaginal products (triple sulfa, sulfanilamide) in addition to oral and parenteral preparations.</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfapyridine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfoxazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (<em>Agenerase</em>)</td>
<td>Precaution</td>
<td>Labeling cautions that the potential for cross-sensitivity with these agents and sulfonamides is unknown. These agents should be used with caution in patients with a sulfonamide allergy. In clinical studies with darunavir plus ritonavir, there was a similar incidence of rash in patients with and without a history of sulfonamide allergy.</td>
</tr>
<tr>
<td>Darunavir (<em>Prezista</em>)</td>
<td>Precaution</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir (<em>Lexiva</em>) (<em>Telzir – Canada</em>)</td>
<td>Precaution</td>
<td></td>
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</table>

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### Drug 1,2,3

<table>
<thead>
<tr>
<th>FDA Product Labeling Recommendations in Sulfonamide Allergy</th>
<th>Comments 1,2</th>
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<tr>
<td><strong>Nonsulfonylarylamines</strong></td>
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<tr>
<td><strong>Carbonic Anhydrase Inhibitors</strong></td>
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</tr>
<tr>
<td>Acetazolamide (Diamox)</td>
<td>Contraindicated, warning (Precaution-Health Canada)⁶</td>
</tr>
<tr>
<td>Brinzolamide (Azopt) (Azarga ¹³=brinzolamide/timolol)</td>
<td>Warning (U.S./Canada Azopt) (Contraindicated-Health Canada)¹³</td>
</tr>
<tr>
<td>Dorzolamide (Trusopt)</td>
<td>Warning</td>
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<tr>
<td>Methazolamide (Neptazane) (Apo-Methazolamide-Canada)</td>
<td>Warning (Precaution-Health Canada)⁶</td>
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<tr>
<td><strong>Cyclooxygenase 2 (COX-2) Inhibitors</strong></td>
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</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>Contraindicated</td>
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<tr>
<td><strong>Loop Diuretics</strong></td>
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<tr>
<td>Bumetanide (Bumex) (Burinex – Canada)</td>
<td>Warning (Contraindication and warning-Health Canada)⁷</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>Precaution</td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
<td>Contraindicated in patients allergic to sulfonylureas</td>
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</tbody>
</table>

Some sources recommend that if a diuretic is used in a patient with a history of sulfonamide allergy, the first dose should be reduced and given under medical supervision. Referral to an allergist may be warranted for patients who have had a severe allergic reaction to a sulfonamide. Ethacrynic acid does not contain a sulfa group and is a possible alternative in sulfonamide-allergic patients. Bumetanide and furosemide product labeling contain statements that patients may also be allergic to these drugs if they are allergic to sulfonamides. One case report suggests cross-sensitivity between furosemide and other sulfonamides. Torsemide is contraindicated in patients allergic to sulfonylureas because its chemical structure is a pyridine sulfonylurea. However, none of the product labeling for sulfonylureas contain statements regarding the use of torsemide. One patient that developed angioedema with torsemide treatment was later found to be sulfonamide-allergic.
### Drug recommendations in sulfonamide allergy

<table>
<thead>
<tr>
<th>Drug1,2,c</th>
<th>FDA Product Labeling Recommendations in Sulfonamide Allergy(^a)</th>
<th>Comments1,2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonsulfonylarylaines (cont.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide (Diabinese) (Apo-Chlorpropamide – Canada)</td>
<td>None</td>
<td>There is one case report of contact dermatitis with tolbutamide in a patient with sensitivity to sulfanilamide vaginal cream. After discontinuation of tolbutamide, therapy was changed to chlorpropamide, which was tolerated without difficulty.</td>
</tr>
<tr>
<td>Glimipiride (Amaryl)</td>
<td>Warning (Contraindicated-Health Canada)(^8)</td>
<td>There is also one case report that describes an allergic reaction to glyburide in a patient with a known allergy to sulfamethoxazole.</td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Glyburide (DiaBeta, others)</td>
<td>Warning (Contraindicated-Health Canada)(^9)</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide (Orinase) (Apo-Tolbutamide – Canada)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Tolazamide (Tolinase)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Thiazides and Related Compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide (Diuril)</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton) (Apo-Chlorthalidone – Canada)</td>
<td>Contraindicated</td>
<td>Some sources recommend that if a diuretic is used in a patient with a history of sulfonamide allergy, the first dose should be reduced and given under medical supervision. Referral to an allergist may be warranted for patients who have had a severe allergic reaction to a sulfonamide. Ethacrynic acid does not contain a sulfa group and is a possible alternative in sulfonamide-allergic patients.</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Contraindicated</td>
<td>Case reports suggest cross-reactivity between indapamide and sulfonamide antibiotics.</td>
</tr>
<tr>
<td>Indapamide (Lozol) (Lozide – Canada)</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Metolazone (Mykrox, Zaroxolyn)</td>
<td>Warning (No recommendation per Health Canada)</td>
<td></td>
</tr>
<tr>
<td><strong>Other Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mafenide (Sulfamylon)</td>
<td>Contraindication, precaution</td>
<td>It is not known whether there is cross sensitivity to other sulfonamides.(^{10})</td>
</tr>
<tr>
<td>Probenecid (Benemid) (Benuryl – Canada)</td>
<td>None</td>
<td>--</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine) (Salazopyrin – Canada)</td>
<td>Contraindicated</td>
<td>Sulfasalazine is broken down in the gut into sulfapyridine and 5-aminosalicylic acid (mesalamine). Sulfasalazine is contraindicated because sulfapyridine is a sulfonylarylamine that is systemically absorbed.</td>
</tr>
</tbody>
</table>
### Nonsulfonylarylamines (cont.)

#### Other Agents (cont.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Product Labeling Recommendations in Sulfonamide Allergy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin (&lt;i&gt;Flomax&lt;/i&gt;)</td>
<td>Precaution (No recommendations per Health Canada)</td>
<td>Cross-reactivity in sulfa-allergic patients rarely reported. Cautious use recommended with serious or life-threatening sulfa allergy.&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tipranavir (&lt;i&gt;Aptivus&lt;/i&gt;)</td>
<td>Precaution</td>
<td>The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir (a protease inhibitor) is unknown.&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Sulfonamide Moiety-Containing Drugs

#### 5-HT Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Product Labeling Recommendations in Sulfonamide Allergy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naratriptan (&lt;i&gt;Amerge&lt;/i&gt;)</td>
<td>None</td>
<td>Sulfonamide group not on benzene ring, FDA concluded no risk of cross-reactivity. A retrospective chart review evaluated patients with a sulfonamide allergy receiving sumatriptan. No allergic reactions were reported during sumatriptan therapy.</td>
</tr>
<tr>
<td>Sumatriptan (&lt;i&gt;Imitrex&lt;/i&gt;)</td>
<td>None</td>
<td>--</td>
</tr>
</tbody>
</table>

#### Other Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Product Labeling Recommendations in Sulfonamide Allergy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibutilide (&lt;i&gt;Corvert&lt;/i&gt;)</td>
<td>None</td>
<td>--</td>
</tr>
<tr>
<td>Sotalol (&lt;i&gt;Betapace&lt;/i&gt;) (Sotacor – Canada)</td>
<td>None</td>
<td>--</td>
</tr>
<tr>
<td>Topiramate (&lt;i&gt;Topamax&lt;/i&gt;)</td>
<td>None</td>
<td>--</td>
</tr>
<tr>
<td>Zonisamide (&lt;i&gt;Zonegran&lt;/i&gt;)</td>
<td>Contraindicated</td>
<td>One small study showed no risk of cross-reactivity when zonisamide was used in patients allergic to sulfonylarylamines.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Information from U.S. product labeling current at time of publication. Health Canada product labelling listed by exception.

<sup>b</sup> A sulfonamide is any compound that contains a S02NH2 moiety. Sulfonamides are divided into three different groups based on chemical structure. The first group, the sulfonylarylamies, have a sulfonamide moiety directly attached to a benzene ring with an unsubstituted amine (-NH2) moiety at the N4 position. The second group, the nonsulfonylarylamines, also have a sulfonamide moiety attached to a benzene ring or other cyclic structure, but they do not have an amine group at the N4 position. The third group, known as the sulfonamide moiety-containing drugs, have a sulfonamide group that is not connected to a benzene ring like in the other groups.<sup>2</sup>

<sup>c</sup> Chart may not include all sulfa drugs currently marketed in the U.S. or Canada.
Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Project Leaders in preparation of this Detail-Document: Sherri K. Boehringer, Pharm.D., BCPS (Original), Stacy A. Hester, R.Ph., BCPS, Assistant Editor (May 2010 update)

References

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Opioid Intolerance Decision Algorithm

For help with dose conversion, please see our chart, “Equianalgesic Dosing of Opioids for Pain Management.”—

When patients say they’re allergic to an opioid, are all opioid analgesics off limits? The key is getting a detailed description of the reaction. Answer the questions below and follow the instructions to find the best options for your patient.

**Check the symptoms the patient describes, and follow the instructions in the far right column.**

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing, itching, hives, sweating, and/or mild hypotension only</td>
<td>Go to A</td>
</tr>
<tr>
<td>Itching, flushing, or hives at injection or application site only</td>
<td>Go to A</td>
</tr>
<tr>
<td>Severe hypotension</td>
<td>Go to B</td>
</tr>
<tr>
<td>Skin reaction other than itching, flushing, or hives (e.g., rash)</td>
<td>Go to B</td>
</tr>
<tr>
<td>Breathing, speaking, or swallowing difficulties</td>
<td>Go to B</td>
</tr>
<tr>
<td>Swelling of face, lips, mouth, tongue, pharynx, or larynx</td>
<td>Go to B</td>
</tr>
</tbody>
</table>

A. These symptoms **may** be due to a pseudoallergy. It’s a result of histamine release, a pharmacologic side effect of some opioids. Options for this patient include:

1. A nonopioid analgesic (e.g., acetaminophen, an NSAID)
2. Avoidance of codeine, morphine, and meperidine, the opioids most commonly associated with pseudoallergy
3. Use of a more potent opioid less likely to release histamine. Potency, from lower to higher:
   - meperidine<codeine<morphine<hydrocodone<oxycodone<hydromorphone<levorphanol<fentanyl
4. If needed, concurrent administration of an antihistamine...an H1 (e.g., diphenhydramine) and perhaps an H2 blocker (e.g., cimetidine)
5. Dose reduction, if tolerated

B. This patient **may** have experienced a true allergy. Options for this patient include:

1. A nonopioid analgesic (e.g., acetaminophen, an NSAID)
2. An opioid in a chemical class **different** from the one to which the patient reacted, with close monitoring:*

   **Phenylpiperidines**: meperidine *(Demerol)*, fentanyl *(Duragesic, Actiq, Sublimaze)*, sufentanil *(Sufenta)*, remifentanil *(Ultiva)*

   **Diphenylheptanes**: methadone *(Dolophine)*, propoxyphene *(Darvon)*

   **Morphine group**: morphine, codeine, hydrocodone *(Vicodin, Lorcet)*, oxycodone *(Percocet, OxyContin)*, oxymorphone *(Numorphan)*, hydromorphone *(Dilaudid)*, nalbuphine *(Nubain)*, butorphanol *(Stadol)*, levorphanol *(Levo-Dromoran)*, pentazocine *(Talwin)*

* Tramadol *(Ultram, etc. [U.S.]; Zytram XL, etc. [Canada]) is contraindicated in patients with opioid allergy per U.S. and Canadian product labeling.23,26 There is not good evidence for cross-sensitivity of tramadol with opioids. However, experts recommend using tramadol only for patients who have mild reactions to opioids. The product labeling for tapentadol *(Nucynta [U.S.]) does not contain this same contraindication, but the FDA considers tapentadol structurally related to tramadol.27 Experts also suggest cautious use of tapentadol in patients with opioid allergy.
Background
Opioid allergy is a common patient complaint. But true allergy is rare. Upon questioning, it often becomes clear the “allergy” is only a side effect, such as stomach upset. But when the symptoms are those associated with allergic-type reactions (e.g., hives), there’s a need to determine which, if any, opioid is safe. To choose a safe alternative, a thorough description of the reaction and an understanding of opioid reactions are needed.

Types of Reactions to Narcotics
Most allergic-type reactions to opioids involve codeine, morphine, or meperidine. A common type of reaction to these opioids is pseudoallergy. Symptoms can resemble a true allergy, but are caused by histamine release from cutaneous mast cells, a nonimmunologic effect. Symptoms of pseudoallergy include itching, flushing, and sweating. Hives, increased heart rate, and low blood pressure can be due to pseudoallergy, but are also seen with true allergy.

Unlike true allergy, prior exposure to the opioid or related opioid is not necessary. In vitro and clinical data suggest risk of pseudoallergy depends on the concentration of the opioid at the mast cell. This is dependent on opioid potency, dose, and route of administration.

True allergy to opioids seems to be IgE-mediated or T-cell mediated. Allergic skin reactions to opioids include hives, maculopapular rash, erythema multiforme, and pustular rash. Bronchospasm is thought to represent true allergy only. Reports suggest angioedema is usually a manifestation of true allergy, but pseudoallergy is also possible.

Narcotic Cross-reactivity
There are three main opioid structural classes. One structurally similar group is comprised of morphine, codeine, hydromorphone, nalbuphine, butorphanol, levorphanol, and pentazocine. Methadone and propoxyphene are in the diphenylheptane class. And meperidine and fentanyl are phenylpiperidines.

Patients allergic to one opioid are thought to be less likely to react to an opioid in a different structural class. But because true allergy is rare, there’s not enough information to assess the chance of cross-reactivity.

It’s important to note there is evidence patients can be allergic to more than one narcotic class. For example, IgE antibodies isolated from a patient allergic to morphine were able to bind to fentanyl. Morphine antibodies have also shown some reactivity with methadone and meperidine.

Diagnosis of Opioid Allergy
It’s important to take steps to avoid labeling nonallergic patients allergic. If the nature and cause of the reaction are not clarified, opioids may be withheld unnecessarily. Even if the reaction is found to be opioid-related, information from the history can be used to choose a safer opioid. For example, history of tolerability of other opioids can be a clue to the mechanism of the reaction, and guide narcotic choice.

Patients should be asked about symptoms, and foods and other medications ingested several hours before the reaction. Also inquire about preceding activities, and the possibility of bites or stings. Medical records pertaining to the reaction, if available, should be reviewed. Alternate diagnoses (e.g., hereditary angioedema, scombroid fish poisoning, carcinoid syndrome) should be considered.

Elevated total IgE levels during the acute reaction suggest true allergy. But IgE could be elevated for reasons unrelated to drug allergy. Tests for IgE to specific opioids have been developed, but are not readily available.

Skin testing has been suggested before using a structurally unrelated opioid in a patient with a serious opioid reaction. But false-positive results due to pharmacologic histamine release have been documented with codeine, morphine, and
Choosing an Analgesic

When choosing an analgesic for a patient with a history of an allergic-type opioid reaction, the benefits of an opioid must be weighed against the risk of a serious reaction.

If the reaction is only flushing, itching, sweating, hives, and/or mild hypotension, the opioid can usually be continued with an antihistamine or dose reduction [Evidence level C; expert opinion].3,4,18

Because pseudoallergic reactions appear to be a function of opioid dose and potency, consider use of a higher potency opioid [Evidence level C; expert opinion]. Start with a low dose [Evidence level C; expert opinion].18 If possible, avoid parenteral administration, or slow the administration rate [Evidence level C; expert opinion].2

Some patients have a reaction under the fentanyl patch. For these patients, spraying triamcinolone nasal spray (Nasacort) to the area before patch application may be helpful [Evidence level C; expert opinion].19

It’s prudent to assume other reactions (e.g., rash, severe hypotension, bronchospasm, angioedema) have an allergic mechanism. If an opioid is necessary, choose one in a different structural class if possible, and monitor the patient closely [Evidence level C; expert opinion].1,4

When choosing an alternative opioid, consider the risks, benefits, and practicality of the drug. For example, the fentanyl patch (Duragesic) is best reserved for chronic pain due to its slow onset of action.20 Duragesic and the fentanyl lozenge (Actiq) are for patients who’ve been taking, at minimum, morphine 60 mg daily or equivalent for a week.21,22 Both methadone (Dolophine) and levorphanol (Levo-Dromoran) must be dosed cautiously. Their long half-lives can cause drug accumulation and CNS and respiratory depression with repeated dosing. And remember that meperidine should be limited to short-term use because of its neurotoxic side effects.20 Tramadol (Ultram, etc. [U.S.]; Zytram XL, etc. [Canada]) is contraindicated in patients with opioid allergy per U.S. and Canadian product labeling.23,26 There is not good evidence for cross-sensitivity of tramadol with opioids. However, experts recommend using tramadol only for patients who have mild reactions to opioids. The product labeling for tapentadol (Nucynta [U.S.]) does not contain this same contraindication, but the FDA considers tapentadol structurally related to tramadol.27 Experts also suggest cautious use of tapentadol in patients with opioid allergy. Propoxyphene and codeine are not recommended due to poor efficacy.24 Pentazocine (Talwin) should be avoided due to psychiatric side effects (e.g., dysphoria).19,24,25 Patients with mild to moderate pain may be best served by acetaminophen or an NSAID.1,4

Conclusions

Most patients who say they’re allergic to an opioid have only experienced a side effect. For patients with a history of allergic-type reaction, options include a nonopioid or a carefully chosen opioid. Potential risks and benefits must be considered.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High-quality randomized controlled trial (RCT)</td>
</tr>
<tr>
<td></td>
<td>High-quality meta-analysis (quantitative systematic review)</td>
</tr>
<tr>
<td>B</td>
<td>Nonrandomized clinical trial</td>
</tr>
<tr>
<td></td>
<td>Nonquantitative systematic review</td>
</tr>
<tr>
<td></td>
<td>Lower quality RCT</td>
</tr>
<tr>
<td></td>
<td>Clinical cohort study</td>
</tr>
<tr>
<td></td>
<td>Case-control study</td>
</tr>
<tr>
<td></td>
<td>Historical control</td>
</tr>
<tr>
<td></td>
<td>Epidemiologic study</td>
</tr>
<tr>
<td>C</td>
<td>Consensus</td>
</tr>
<tr>
<td></td>
<td>Expert opinion</td>
</tr>
<tr>
<td>D</td>
<td>Anecdotal evidence</td>
</tr>
<tr>
<td></td>
<td>In vitro or animal study</td>
</tr>
</tbody>
</table>

Project Leader in preparation of this Detail-Document: Melanie Cupp, Pharm.D., BCPS

References


Cite this Detail-Document as follows: Analgesic options for patients with allergic-type opioid reactions. Pharmacist’s Letter/Prescriber’s Letter 2006;22(2):220201.
Investigating Possible Drug Allergy or Sensitivity

Drug allergies noted on a patient’s chart or medication profile can be somewhat nebulous, with no description or just a single word such as “rash” or “nausea” describing the event. This may lead to inappropriate avoidance of the offending drug or other drugs, compromising or unnecessarily complicating patient care. For example, a patient with a codeine allergy and no specific reaction noted on his or her profile might receive inferior pain relievers such as propoxyphene, when the reaction is simply an upset stomach. On the flipside, it’s important to have accurate documentation of allergies so other drugs that could cause a reaction can be avoided. For some drugs such as aspirin, a sensitivity reaction may not be an actual allergy. Aspirin sensitivity involves symptoms that are respiratory in nature, such as rhinitis and worsening of asthma, or skin manifestations, such as urticaria and angioedema. Aspirin sensitivity is due to COX-1 inhibition, and not to an actual immune response. Because NSAIDs also inhibit COX-1, patients who have aspirin sensitivity are likely to also have sensitivity to NSAIDs. However, the chance for cross-reactivity between aspirin and NSAIDs in a patient with a true allergic reaction to either is less likely.

Prior to treating patients who report a drug allergy, a thorough history of the patient’s allergy should be obtained. Example questions the patient should be asked are included below. However, keep in mind there are times when a patient will require intricate diagnosis and testing for drug allergies, such as when skin testing for penicillin-specific IgE is indicated.

Be aware that the significance of responses to these questions can vary according to the drug that caused the reaction. Also be aware that individuals who have an allergy to one drug are more likely to have other drug allergies than those who aren’t allergic to any drugs at all.

Is there any medicine you cannot take for any reason? By what route did you receive the drug?

(Identifying all problematic drugs, whether due to allergy or intolerance, is important. In some instances, a perceived "intolerance" problem may be minimized or avoided with counseling [e.g., take with food] or modification of therapy [e.g., dosage reduction].)

Why was the medication prescribed?

How long ago did the reaction occur?

(The longer the time from the original administration of an allergen to the next administration, the less chance an IgE-mediated, or Type I, reaction will recur. This includes reactions such as hives and anaphylaxis. About 70% of people with penicillin allergy lose their allergy after five to ten years.)
Can you describe the reaction? How was the reaction managed?
(The most common allergic reaction to a drug is measles-like rash. Symptoms that could be suggestive of anaphylaxis include sense of warmth, flushing, itching, hives, facial or throat swelling, asthma or wheezing, nausea or vomiting, light headedness from low blood pressure, or abdominal cramping.)

How soon after taking the drug did your reaction occur?
(Onset of drug allergy usually happens several days to several months after starting a drug. Anaphylaxis usually occurs within one hour after a drug is taken.)

When the offending drug was stopped, what happened?
(An allergic reaction should subside within several days to weeks after the drug is stopped.)

Were you taking any other medications, including OTCs or supplements, at the same time the reaction occurred? Had you ingested any type of food that may have caused the reaction?
(Consider the possibility that the reaction could have been related to the pharmacological action of, or reaction to, another substance.)

Have you since taken the SAME drug? If so, what happened?

Have you taken a SIMILAR drug since the reaction happened? If so, what happened?
(Consider asking a patient who had a reaction to penicillin if he or she has taken a cephalosporin, or a patient who had a reaction to an opioid if he or she has taken a different opioid.)

Have you ever had the SAME reaction with a DIFFERENT drug?
Making sure that you have a patient’s up-to-date allergy information is a vital step in helping to ensure safe medication use. In fact, more than 200,000 people are treated in emergency rooms each year for drug allergies.

The range of “allergic” reactions that patients experience can vary widely. Around one in ten reported side effects are actually drug allergies. Some patients will report side effects, like nausea or upset stomach, as allergies. But these reactions aren’t allergies at all. Other drug reactions, such as swelling and shortness of breath, ARE allergies. These reactions can indicate that certain drugs may cause life-threatening reactions in certain patients.

A true drug allergy happens as a result of activity of the immune system. Allergic reactions can occur as soon as a drug is taken, or days after. The different types of antibodies that are involved determine how long the reaction takes. Reactions indicating a true drug allergy include hives, rash, difficulty breathing, speaking, or swallowing, wheezing, and severe low blood pressure. A severe allergic reaction that includes these symptoms is sometimes referred to as “anaphylaxis” or an “anaphylactic reaction.” Anaphylaxis can be deadly.

Compared to drugs taken orally, drugs that are either injected or applied to the skin are more likely to cause allergic reactions.

Besides the wide range of reactions that can be reported by patients, specific drugs that can or can’t be used in a patient with a particular allergy can be confusing. Allergies to aspirin, opioids (e.g., codeine, hydrocodone, morphine, etc.), penicillins (e.g., amoxicillin, Augmentin, Clavulin [Canada]), and sulfa drugs (sulfamethoxazole, which is in Septra and Bactrim DS) are among the most commonly reported. Penicillin is THE most common drug allergy and is reported by about one in ten patients. About one in ten adults with asthma have an allergy to aspirin.

Essentially, evaluating the appropriateness of therapy for patients with drug allergies involves determining if the reaction is actually an allergy, and which drugs, if any, should be avoided. Usually, when a patient has a true allergy to a drug or class of drugs, the pharmacist can recommend another drug that will treat the patient’s condition safely.

A new patient, Katherine Katz, comes in to your pharmacy. You ask her for all the usual information, including drug allergies. She says that she is allergic to penicillin and Tylenol #3 and hands you the following prescription.

Prescription interpretation:

Keflex 500 mg twice daily for ten days. When you enter this prescription into the pharmacy computer system, you get a warning that the patient could have an allergic reaction to Keflex. You know that cephalexin is not a penicillin, but you advise the pharmacist that Ms. Katz has a penicillin allergy.
What additional information do you need to get from Ms. Katz?

Ask Ms. Katz what type of reaction she had. The pharmacist will need this information to decide whether her reactions were actually allergies, or just a side effect of the medication, or an intolerance to the drug.

Ms. Katz states that she had hives from penicillin and amoxicillin in the past and that Tylenol #3 makes her “very nauseous,” but she’s never had a rash or any other reaction to it.

What information should be entered into the computer based on Ms. Katz’s history?

It is very important to keep good records of a patient’s reactions to drugs. In this case, “penicillin” should be entered as a drug allergy and a note can be added to Ms. Katz’s patient profile stating that she reports extreme nausea with Tylenol #3. Based on Ms. Katz’s description of her reaction, an allergy to Tylenol #3 should NOT be entered.

The distinction between the two types of entries is important. Flagging penicillin as an allergy will ensure that the pharmacy computer system is also scanning Ms. Katz’s future prescriptions for drugs that are similar to penicillin, like amoxicillin or ampicillin, and will increase the likelihood of avoiding a future reaction to one of these meds.

However, the same is not true of Tylenol #3, since Ms. Katz is reporting an intolerance or a side effect to this medication, and not a true drug allergy. Making a note in the computer alerts the pharmacist of this side effect and will prompt the pharmacist to recommend something that will help Ms. Katz avoid it in the future. For example, if Ms. Katz had a prescription for an opioid similar to codeine which is found in Tylenol #3, the pharmacist might recommend that she take the drug with food to minimize the nausea.

Ask your pharmacist for guidance if you are unsure if patients are describing a true allergic reaction or a side effect or intolerance. It can sometimes be hard to differentiate between these.

When a patient reports an allergy to one drug, what other drugs should also be avoided?

When a patient is allergic to a particular drug, it’s usually best for that drug to be avoided unless absolutely necessary. Drugs in the SAME CLASS should generally be avoided as well.

We’ll use sulfa drugs to illustrate. For example, a patient who is allergic to Bactrim (sulfamethoxazole/trimethoprim) will probably also be allergic to other sulfa drugs, like sulfadiazine (Silvadene) and sulfisoxazole.

Keep in mind that the term “sulfa drug” refers to drugs that are classified as sulfonamides, with a specific chemical structure. Sometimes, there’s confusion over whether or not an allergy to sulfa drugs means that a patient is also allergic to sulfate, as in morphine SULFATE. The chemical structure of sulfate is not the same as the structure of sulfonamides, so an allergic reaction isn’t expected.

What is allergic cross-reactivity?

When a patient has had an allergic reaction to a particular drug, there’s a chance that he or she might also have an allergic reaction to drugs with a similar chemical structure. This is referred to as “cross-reactivity.” For example, cephalosporins (e.g. cephalexin [Keflex], cefuroxime [Ceftin, Zinacef], etc.) are chemically similar to penicillins. Around one out of 100 patients who are allergic to penicillin will have an allergic reaction to a cephalosporin drug.

Carbapenem antibiotics (e.g., doripenem [Doribax], ertapenem [Invanz], imipenem [Primaxin], meropenem [Merrem]) and monobactam antibiotics (e.g., aztreonam [Azactam]) are also chemically similar to penicillins. Around one out of 100 people with a true penicillin allergy will have a reaction to a carbapenem. In the general population, the risk may be slightly less for monobactams.

Cross-reactivity can also vary between different subgroups of the same drug class. Opioid analgesics are a good example. The opioid analgesic drug class can be subdivided into three distinct chemical/structural classes. Morphine, codeine, hydrocodone, and oxycodone are all in the same chemical class. Meperidine and fentanyl are in a different chemical class. Methadone and propoxyphene
are in yet another chemical class. For patients with opioid allergies, a good choice might be another opioid that is not in the same chemical class as the offending opioid. The pharmacist might recommend a drug from a chemical class other than the one the patient is allergic to.

Some drugs that don’t have “sulfa” in the name might be dangerous for patients with sulfa allergy. These include celecoxib (Celebrex), some diuretics, some medications for HIV, and zonisamide (Zonegran). The risk for cross-reactivity in patients with sulfa allergies is variable with these drugs.

The decision about whether it is okay to use drugs from a different class with a similar chemical structure can depend on how severe a patient’s reaction to a particular drug is and how badly they need to take the drug to which they may react. For example, a pharmacist might recommend against using Keflex in a patient who had a life-threatening allergic reaction with penicillin. On the other hand, using Keflex would be considered safer in a patient who only had a rash with penicillin.

Alert your pharmacist to any drug allergy alerts that show up in your computer system, even if they do not seem to be for the same drug. The alert might be caused by a cross-reactivity between two drugs. An alternative drug might be better for the patient to avoid a potential reaction, as in the case of the patient with the life-threatening penicillin allergy above.

Verify allergy information at every opportunity to make sure you have the most accurate and updated information possible in the computer to detect any potential reactions.

What if a patient MUST have a medication that he or she is allergic to?

If a patient has had a serious allergic reaction to a medication that he or she MUST have, there are times when a “desensitization protocol” can be used. Desensitization involves initially giving a patient a very small amount of drug, and repeating administration with increasingly larger amounts. Eventually, normal doses of the drug can be tolerated. However, hypersensitivity to a drug will usually return after the course of treatment is stopped.

Normally, desensitization is supervised by an allergist. There’s a chance that the patient could have a severe reaction at any time. Appropriate precautions, like ensuring immediate access to emergency medications, must be taken.

Although a skin reaction associated with use of a drug usually indicates an allergic reaction, there are exceptions. What are they?

It’s possible for a patient to have a skin reaction, like flushing, hives, or itching, after taking a medication that he or she is NOT allergic to. One such reaction is called a “pseudoallergy.” Pseudoallergy can occur with drugs that cause the release of some inflammatory chemicals in the body, such as histamine.

An example of pseudoallergy is a rash caused by infusion of the injectable antibiotic, vancomycin. This reaction is called “red man syndrome.” Patients will most often have a red rash on the neck and shoulders. Slowing the infusion rate of vancomycin in patients who have experienced red man syndrome can help prevent it from happening again.

A histamine-related pseudoallergy can occur when patients take some opioids for pain, such as morphine. When this happens, certain opioids might need to be avoided, or an antihistamine (e.g., diphenhydramine [Benadryl], etc.) can be given to help minimize the reaction.

Patients may also experience “photosensitivity” when taking some drugs. Photosensitivity is not necessarily an allergic reaction. This increased sensitivity of the skin to the sun’s effects can result in reddening of the skin or sunburn and is sometimes seen with sulfonamide antibiotics, isotretinoin (Accutane), and tetracyclines.

Check out “Management of Common Skin Diseases” for examples of skin reactions to drugs that ARE NOT caused by allergies.

The pharmacist approaches Ms. Katz, and Ms. Katz explains that she had hives with penicillin. She says that it was probably 30 years ago since this happened. She also tells the pharmacist that she has had Keflex before with no problems. The pharmacist tells her that there is a small chance that she will
have a reaction with the Keflex, but that he feels comfortable dispensing it to her. She agrees that she is comfortable taking Keflex. The pharmacist tells Ms. Katz that if she has any kind of reaction, from hives to shortness of breath or swelling, to call her provider immediately.

**Are food allergies important to know?**

Yes, although food allergies are only an issue with a few drugs. There are actually a few medications that are contraindicated in patients with certain food allergies. This is usually not because of the drug itself, but instead, because of the drug formulation. For example, *Atrovent* (ipratropium) and *Combivent* (ipratropium/albuterol) inhalers both contain soy lecithin as a suspending agent. Soy and peanuts are in the same plant family. Patients who are allergic to peanuts might also react to soy. The newer injectable drug *Cleviprex* (clevidipine), which is for blood pressure lowering, is formulated with both eggs and soy. It’s contraindicated in patients who have soy or egg allergies. Patients with egg or gelatin allergies shouldn’t get the intranasal flu vaccine, *FluMist*.

Remember that latex allergy should also be noted. Some medication containers, like vial stoppers, contain latex. However, in the past decade or so, manufacturers have made drug packaging safer for patients with latex allergy.

If a patient reports a food or latex allergy check with your pharmacist about the best way to enter this into the pharmacy computer system. Many systems allow food or other allergies to be entered in the same way as a drug allergy, so that the allergy can be checked against drugs that shouldn’t be used.

**How does drug allergy monitoring differ in the hospital setting?**

In the hospital, a patient’s allergy information is usually recorded or entered into the computer system by a nurse or provider. However, pharmacists may need to request more information from the patient, a family member, or nurse, if more details such as the specific reaction are needed. Alert the pharmacist if you notice that drug allergy is missing from the patient’s profile, chart, med order, etc.

No matter the practice setting, medications should not be dispensed until allergy information is provided. There are very rare exceptions to this rule. One exception would be for administration of life-saving medications when a patient is unconscious and allergy information is not immediately available, as for a trauma patient before family members have arrived. For this reason, patients who have experienced very severe allergic reactions should consider wearing a *Medic Alert* bracelet or necklace which lists his or her allergies.

When you encounter patients who have very severe allergic reactions to drugs, remind them that the *Medic Alert* bracelet or necklace could provide that important information in an emergency situation.

**Resources**


