

A Practical Drug Allergy Update: What You Need to Know About Drug Allergies But Did Not Learn in Medical School

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What Is a Drug Allergy?

Formally, a drug allergy is a clinically significant adverse reaction mediated by IgE that is reproducible on rechallenge. To cause a drug allergy, a drug must be an intact multivalent allergen, such as a protein with a molecular weight greater than 5000, or be able to haptenate an endogenous protein. Functionally, all drugs listed in the “drug allergy” section of a medical record are drugs for which the patient’s physicians believe exposure carries significantly greater risks than benefits, judgments based primarily on what happened the last time the patient took the medication or on some underlying patient-specific condition. The majority of adverse drug reactions and thus reports of drug allergy in the medical record are nonallergic and even not immunologically mediated. There are other significant, immunologically mediated adverse drug reactions in addition to IgE-mediated drug allergy. Drug-specific IgG can cause nephritis, hemolytic anemia, and reactions similar to serum sickness. Delayed-onset adverse drug reactions mediated by T cells are primarily cutaneous and cannot result in acute anaphylaxis. Individuals with reactions mediated by IgG or T cells cannot be desensitized. T-cell-mediated reactions can be blunted with corticosteroids. Fortunately many such reactions are quite mild. Some can be identified by patch testing.

Risk Factors for Multiple “Allergies” in Medical Records

I looked at the “drug allergy” field in HealthConnect, the electronic medical record system for Kaiser Permanente (KP), for 411,543 San Diego County KP members who had at least one outpatient visit in 2007. There were 275 individuals who reported 10 or more drug “allergies”: 92% were women, mean age 67 ± 15

years, and 60% had a diagnosis of depression or serious mental illness. Fifteen of these patients had been seen in the Allergy Department and had undergone at least one allergy test: 12 had negative penicillin skin tests and oral challenges, two had negative lidocaine skin test and challenge, and one had a negative latex blood allergy test.

Risk Factors for Antibiotic Allergy

Antibiotics accounted for the majority of drug allergy entries. Penicillins, sulfonamides, cephalosporins, tetracyclines, macrolides, and quinolones were the classes of antibiotics evaluated. Antibiotic classes with higher historical use have higher “allergy” prevalence. Women take more antibiotics than men do and have higher “allergy” prevalence rates for all classes of antibiotics. There is a steady increase in antibiotic “allergy” prevalence with aging for both sexes. Women also have higher “allergy” incidence rates for all classes of antibiotics. Antibiotic “allergy” incidence in women is highest for sulfonamides, at 3.4%, compared with 1% to 1.5% for all other classes of antibiotics. Antibiotic “allergy” incidence in men is also highest for sulfonamides, at 2.2%, compared with 1.1% for penicillins and 0.5% to 0.6% for all other classes of antibiotics. Female sex, higher use, and increasing age are the primary factors that account for higher antibiotic “allergy” prevalence.

How to Minimize the Number of Drug Allergies a Person Develops

The single most important thing that clinicians can do to minimize the number of drug “allergies” that patients develop is to not use antibiotics outside the setting of bacterial infections. Most often, nasal pharyngitis and other acute upper respiratory infection syndromes are

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not helped by antibiotics. Chronic or recurrent sinus disease should be documented radiographically and appropriately treated with nasal saline lavage, a short course of oral steroids, and at least three weeks of an appropriate antibiotic. Repeated empiric short-term antibiotic therapy for individuals with facial pain contributes to antibiotic resistance and adverse drug reactions. Often facial pain attributed to sinusitis is migraine or another headache syndrome worsened in the setting of an acute viral infection. Also, most ear pain is not helped by antibiotics. Even though a patient expects or even demands an antibiotic for symptoms associated with upper respiratory infection, the chance that you will cause a problem by giving an antibiotic is often greater than the chance that you will ameliorate symptoms.

How to Deal with Individuals Who Are “Allergic” to “Everything”

Individuals who report multiple allergies should be evaluated by an allergist. Though it is important to avoid reexposure to an antibiotic when there is a high probability of another reaction, it can also be just as important not to needlessly avoid the preferred antibiotic for an infection because of an inaccurate drug allergy record. Not giving the drug of choice when it could be tolerated can result in more severe problems even when an alternative antibiotic is given. Think of vancomycin-associated red man syndrome and the growth of *Clostridium difficile* after broad-spectrum antibiotics are used when a more appropriate narrow-spectrum penicillin could have been used.

Specific Actions the Allergy Department Can Take for Individuals with Possible Drug Allergies

Skin testing is available for penicillin and local anesthetics.

Penicillin skin testing can be safely done in advance of need. There is no significant resensitization with penicillin skin testing. Penicillin allergy is becoming less common than it was in the 1980s and 1990s. Fewer than 1 in 20 individuals with a history of penicillin allergy had positive skin test results in 2008. Blood allergy tests for penicillin allergy have no clinical utility and should never be done.

There is no clinically significant penicillin–cephalosporin allergy cross-reactivity. Even patients whose penicillin skin test results are positive can be safely given cephalosporins. The current drug interaction software in HealthConnect must be changed to reflect this. Cephalosporin skin testing has not been adequately

validated, and specific cephalosporin allergy is rare. Patients who have had an adverse reaction to a particular cephalosporin that could be immunologically mediated should avoid that particular cephalosporin and cephalosporins and other β -lactams that share the same side chains.

Fluoroquinolone skin testing is not useful. There is significant intraclass cross-reactivity with fluoroquinolone-associated reactions, and thus the entire class should be avoided after a significant reaction to one class member.

Macrolides are intrinsically irritating to the skin and thus cannot be effectively used as skin test reagents.

Local anesthetic provocative dose testing should be done on all individuals with a history of local anesthetic allergy. Virtually none of them will be found to be truly allergic. A very few will have an IgE-mediated allergy to methylparaben, the usual preservative in multidose vials. Some patients will have a contact sensitivity to local anesthetics but will be able to tolerate parenteral local anesthetics.

Blood allergy testing, enzyme-linked immunosorbent assay [ELISA] or ImmunoCAP [Phadia, Uppsala, Sweden], should be done on everyone with a history of latex allergy. Those with positive ELISA findings for latex should avoid natural rubber protein containing latex. Those with delayed-onset rashes and negative ELISA findings for latex should consider undergoing patch testing for contact dermatitis.

Challenge tests are available for individuals with a history of certain sulfonamide antibiotics and for adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).

With sulfonamide antibiotics, the reaction rate with rechallenge is about 20%. The widespread use of sulfonamides for the treatment of urinary tract infections probably contributes to the very high prevalence rates of sulfonamide antibiotic “allergy” in older women. Because these antibiotics are becoming an important treatment option for methicillin-resistant *Staphylococcus aureus*, consideration of less widespread use of them for routine urinary tract and upper respiratory tract infections may be warranted.

Individuals with NSAID sensitivity, nasal polyps, sinusitis, and asthma should be evaluated by an allergist. Aspirin desensitization is available and significantly helps these individuals.

Many other people have a history of hives or angioedema associated with NSAIDs; they should also be evaluated by an allergist. Many will be able to tolerate reexposure to certain NSAIDs. Individuals with active

chronic urticaria, defined as recurrent hives for more than six weeks, and/or angioedema may not be able to tolerate reexposure to any NSAIDs, until the chronic urticaria resolves.

Specific allergy testing or rechallenge is inappropriate for patients with any of the following histories: Stevens-Johnson syndrome, toxic epidermal necrolysis, hemolytic anemia, nephritis, hepatitis, or oral and/or skin blisters associated with or attributed to previous drug use. Such individuals should continue to avoid the specific drug or class of drugs implicated. No test provides useful information in these situations, and the risk presented by rechallenge is too great. These patients may still benefit from an allergy consultation, particularly if their medical records list multiple drug “allergies.”

Patients who have a history of anaphylaxis, respiratory problems, hives, swelling at local injection sites, other rashes, gastrointestinal symptoms, unknown index symptoms, and other mild symptoms not specifically excluded here can have allergy testing if available, and they could potentially be rechallenged or desensitized if necessary. ❖

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Alliance

Too often a prescription signals the end to an interview rather than the start of an alliance.

— Barry Blackwell. *Drug therapy: patient compliance.*
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