

Should Antibiotic Allergy Alerts Be Alarming?

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Abstract: Allergies to various antibiotics are reported by a substantial proportion of patients. As a result, clinical decision support programming generates frequent warnings when prescribing within electronic medical records. For a variety of reasons, the majority of these warnings may be inappropriate. Our improved understanding of the underlying physiology of allergic processes reveals that the majority of cross-reacting antibiotic allergies are implausible. Appropriate history taking and workup can invalidate many more warnings. Electronic medical records ideally should permit documentation that would facilitate more accurate entry and eliminate similar future warnings.

Key Words: antibiotic allergy, beta lactams, clinical decision support, drug intolerance, electronic medical record, sulfa antibiotics

Among medications, antibiotics traditionally have been ranked among the most likely to cause significant allergic reactions. In a large managed care population, antibiotics accounted for more than half of the reported drug allergies, with a prevalence of 9% for penicillins, 5.4% for sulfa antibiotics, and 1.3% for both cephalosporins and macrolides.¹ Furthermore, medications are the second most common cause of anaphylactic reactions, after foods.² In a European case series of 333 drug-induced patients having anaphylaxis identified by the Allergy Vigilance Network, antibiotics were implicated in almost half of the cases, with β -lactams representing the largest single cause.³

One of the reasons that electronic medical records (EMRs) are touted as agents that improve patient care and safety is the ability to incorporate clinical decision support. This term refers to the array of computer programming embedded within EMRs which permits real-time comparison of broad clinical databases with patient-specific data to offer information that may improve patient outcomes. This information includes warnings for drug allergies and other factors like drug–drug interactions and drug duplication alerts. Theoretically, use of these tools should reduce markedly the number of adverse drug events that result from these kinds of issues; however, the data are not necessarily clear

in demonstrating this.^{4–6} Although many investigators report changing prescribing practices, demonstration of reduction in actual adverse events is sparse.

Many factors are involved in the difficulty in clinical decision support systems' achieving their goal. One of the more potentially problematic issues is that warnings frequently are ignored. Various studies have reported prescriber-override rates ranging from 53% to 94%.^{7–10} When broken down by type of warning, rates were typically similar. As examples, drug–drug interaction warnings were overridden between 60% and 95% of the time and drug allergy warnings were overridden between 63% and 91% of the time in these studies.^{7–10} In spite of this, where warnings were overridden, adverse reactions were uncommon in patients, ranging from 2.5% to 6%.^{7,11} These rates were found to be indistinguishable from the rates of adverse reactions when warnings were accepted.

Given that the warnings are ignored so frequently and with so little measurable impact, one must assume that many warnings are improper or unnecessary. One review of warnings provided to primary care practitioners in Boston revealed that 36.5% of warnings were invalid and 95.6% of overrides of even valid warnings were justified.⁷ Certainly some of the excess warnings could be reduced through better programming; however, drug allergy warnings in particular have issues that are unlikely to be amenable to more judicious coding. As such, prescribers and pharmacists must have an understanding of when it is appropriate to override allergy warnings and when it is not.

Key Points

- Although many patients report allergies to antibiotics, the majority of these allergies are not verified upon subsequent evaluation.
- Allergy warnings based on cross-reactions to small drug structures, such as a β -lactam ring or a sulfonamide group, almost universally are incorrect. Cross-reaction can occur with sterically similar side chains or larger structures such as sulfonylarylamine groups.
- Accepting allergy warnings “just to be safe” is not safe.
- Allergy warnings should be evaluated, first, with a proper history, followed sequentially by skin testing when possible, and a drug provocation test if needed. If the evaluation is negative, then the allergy should be removed from the medical record.

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Mechanisms of Drug Allergy

The largest single problem in computerized warnings for drug allergy is described by the programmer's axiom GIGO—garbage in, garbage out. Although many patients may report drug allergies, relatively few actually have them. Instead, any form of adverse reaction to a medication often is branded an allergy. Adverse reactions may include headache, nausea, vomiting, diarrhea, or constitutional symptoms. As a result, when patients who report penicillin allergies are evaluated by skin testing, fewer than 5% to 10% actually are positive.¹² Similarly, only 3% of adverse reactions to trimethoprim-sulfamethoxazole are estimated to be true hypersensitivity reactions.¹³ A review of macrolide allergies suggested that only 3% to 17% of reported macrolide allergies are caused by true hypersensitivity reactions.¹⁴ Improper documentation of adverse reactions is promulgated in many EMR systems, which mandate documenting any intolerance in an allergy field. Furthermore, many EMRs permit entering an allergy in the document without a description of the reaction. The absence of a description makes it impossible to immediately distinguish allergies from intolerances. It is understandable that many in the lay public may fail to distinguish between an intolerance and an allergy. It is a grievous error, however, to force healthcare professionals to equate the two in their formal documentation. Distinct fields for drug allergy and drug intolerance should be the standard form of documentation within EMRs.

These documentation errors typically are compounded in clinical decision support programming by issuing warnings against the use of drugs that may potentially cross-react with the "allergy." With respect to antibiotics in particular, much of the reported cross-reactivity is the result of outdated studies, case reports, and incorrect theory (see below). Indeed, rates of adverse reactions to drugs that cross-react with penicillins or sulfa antibiotics are no higher than adverse reactions to unrelated drugs in patients with those reported allergies.^{15,16}

A true allergy, as described in the International Consensus on Drug Allergy written by the International Collaboration in Asthma, Allergy, and Immunology, is an immune-mediated response, involving immunoglobulin (Ig) or lymphocytes.¹⁷ Formally, allergies are a subset of drug hypersensitivity reactions, which also include similar reactions wherein an immunological mechanism cannot be established. Formal diagnosis of drug allergy should involve a careful evaluation of clinical history, skin testing, when appropriate, and a drug provocation test under controlled circumstances. Unfortunately, this is not frequently performed. As an illustration, of the approximately 25 million Americans who report a penicillin allergy, <0.1% undergo allergy testing annually.¹² (Granted, the development of allergies is a complex physiologic process and its evaluation can likewise be complex.)

The β -lactam ring on the penicillin opens rapidly under physiologic conditions, which forms a stable penicilloyl group that can conjugate to protein. Only then is the conjugated hapten large enough to generate production of an antibody. Given the

fact that the β -lactam ring is opened in the majority of antigenic molecules, it follows that antibodies against the β -lactam ring are uncommon. Most IgE antibodies, which are necessary for type I anaphylactic reactions, are instead directed against the penicilloyl group containing the 5-membered thiazolidine ring or the variable R side chain.

The process of generating potential determinants for cephalosporins is less well defined. Like penicillins, the β -lactam ring does open, allowing protein conjugation; however, the analogous cephalosporoyl form is inherently unstable. It rapidly degenerates into a wide variety of other forms. The R1 and R2 side chains are retained, and it is believed that these are the moieties responsible for the generation of most IgE antibodies in cephalosporin allergy. Evidence accordingly suggests that allergic responses to differing cephalosporins occur almost exclusively among those with shared R groups.¹⁸

The distinction in these processes reveals that the reported 10% cross-allergy between penicillins and cephalosporins is a myth. Researchers in the 1970s reported that among patients who reported an "allergy" to penicillin, 7.7% to 8.1% of them subsequently developed "allergic" reactions after taking cephalosporins.^{19,20} A portion of the apparent problem can be explained by the imprecise definition of allergy that was used. Another portion can be attributed to contamination of early cephalosporins with penicillins; most of the rest can be explained by the presence of some R groups that are common to both penicillins and early cephalosporins. Many of the early cephalosporins (eg, cephalothin, cephalixin) had R groups that were either similar or identical to R groups in penicillin or the aminopenicillins (Table). Although many, such as cephalothin, have since been discontinued, they were the most commonly used at the time the cross-allergy paradigm came into being. Newer cephalosporins with unrelated R groups have been proven not to increase the risk of allergic response in patients who are allergic to penicillin.²¹

The process of generating antigenic determinants to sulfonamide antibiotics is similarly suboptimally defined. The presence of a primary arylamine in the N4 position from the sulfonamide group appears to be required both for antibiotic activity and for haptization^{22,23}; however, it is not the moiety typically recognized by antibodies. Instead, the heterocyclic aromatic ring attached to the N1 position of the sulfonamide is what is identified by most IgE antibodies from the sera of allergic patients.^{24,25}

Table. β -lactam antibiotic groups that may cross-react based on sterically similar side chains

Penicillin	Ampicillin	Aztreonam	Cefepime	Cefuroxime	Cefdinir
Cefoxitin	Cephalexin	Ceftazidime	Ceftriaxone	Cefoxitin	Cefixime
	Cefaclor		Cefotaxime		
	Amoxicillin		Cefpodoxime		
	Cefprozil		Cefditoren		
	Cefadroxil		Ceftazidime		
			Cefuroxime		

Unsubstituted sulfonamide groups, as seen in sulfanilic acid, do not react with the antibodies. As a consequence of this, it is highly unlikely that there would be any anaphylactic cross-sensitivity between drugs that simply contain a sulfonamide group. Although differing sulfa antibiotics may cross-react by virtue of having a common N4 arylamine and some similarities in the N1 rings, evidence shows sulfonamide nonantibiotics do not appear to cross-react because they lack those moieties.

Anaphylactic reactions are not the only form of hypersensitivity reactions that can occur with sulfonamide antibiotics. One of the more common presentations is a delayed reaction, typically fever with a maculopapular or morbilliform rash. Rarely this can have additional systemic involvement. Even more rarely, sulfonamide antibiotics can cause Stevens-Johnson syndrome. These reactions appear to be mediated through T cells; the process appears more variable, however.²⁶ Unlike many antigens, cognate T cells that recognize the epitope can be stimulated either by antigen-presenting cells or by direct interaction of the sulfonamide antibiotic with either the T-cell receptor protein or the major histocompatibility protein. Depending on the subtype of T cell, variable inflammatory and cytokine responses can occur, which can then result in differing clinical symptoms. Regardless of which process stimulates the T cells, activation does require more than just a sulfonamide moiety. The entire sulfanilamide structure is required, with the additional N1 side group sometimes being necessary as well; therefore, once again, the sulfonamide nonantibiotics do not cross-react to produce an immune response. Indeed, the large majority of reported sulfa cross-reactivity stems from case reports or case series using ill-defined or undefined immunologic verification.²⁷

Although the specificity of the antigenic process seems to largely preclude cross-reactivity, it does not necessarily preclude additional reactivity. This is illustrated by two studies from the UK General Practice Research Database. Strom and colleagues reported that among patients with a reported history of allergic reaction to a sulfonamide antibiotic, their odds of having a reported allergic reaction to a penicillin were higher than having an allergic reaction to a sulfonamide nonantibiotic (14% vs 9.9%).¹⁵ Conversely, Apter and colleagues demonstrated that among patients with reported histories of allergic response to penicillins, the likelihood of a subsequent allergic reaction to either cephalosporins or sulfonamide antibiotics was similar.¹⁶ These and other results raise the possibility of patients with an increased chance of allergic reactions to any exogenous agent, known as the multiple drug intolerance syndrome. Formally, this is defined as an intolerance to three or more unrelated medications, and prevalence between 2.1% and 4.9% has been reported.^{28,29} Given the imprecise nature of so-called drug allergies, it is debatable whether there is a common pathophysiologic underpinning to these reactions (eg, a “promiscuous” human leukocyte antigen genotype). It is clear that patients meeting these criteria are more likely to demonstrate an intolerance to new medication, however. As such, substituting an unrelated drug in place of a theoretically “cross-reacting” drug offers no demonstrable benefit.

Management of Allergic Warnings

With awareness of the limitations of the data entry and an understanding of the antigenic processes, one may take a more thoughtful approach to antibiotic allergy warnings from an EMR. In discussing such warnings, one must first discuss what not to do, which is to simply take it at face value. The use of alternate, typically broad-spectrum agents “just to be safe” does not improve safety. This is illustrated in a case-control report using southern California Kaiser Foundation hospital admissions.³⁰ Compared with matched control patients, patients with a reported “penicillin allergy” were treated with more fluoroquinolones, vancomycin, and clindamycin and had an increased risk of developing vancomycin-resistant enterococci (30.1%), *Clostridium difficile* (23.4%), and methicillin-resistant *Staphylococcus aureus* (14.1%). Furthermore, cases had 0.59 (95% confidence interval 0.47–0.71) more total hospital days. This extra hospitalization was estimated to cost the healthcare system > \$64 million in the 3-year study window. Safety concerns can be identified even for seemingly benign activities as single-dose antibiotics for endocarditis prophylaxis. A UK study revealed markedly higher adverse effects when using clindamycin rather than amoxicillin (frequently done in patients who are “penicillin allergic”), driven mostly by an increase in *C. difficile* infections.³¹ Given that >90% of “penicillin allergic” patients are in fact not allergic, this exposes large numbers of individuals to excess risk and expense.

According to the International Consensus on Drug Allergy,¹⁷ the first thing that a clinician should do when faced with an allergy warning is to obtain a good history, including the specific identity of the inciting antibiotic and the exact nature of the reaction. Although this is obvious, often it is overlooked. The situation is exacerbated by the fact that many EMRs not only permit the absence of such documentation on entry but also may make it difficult to edit allergy entries. As such, even if the information is obtained, it may be difficult to communicate the knowledge to future providers.

Severe disseminated reactions such as Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms must be regarded as evidence of a hypersensitivity reaction; however, even symptoms that may be consistent with anaphylaxis, such as urticaria or mild bronchospasm, are not absolute contraindications. Although they should be taken into account and discussed with the patient, nonspecific complaints such as nausea, headache, or diarrhea regarding a medication should not completely preclude use of the medication a second time, much less the use of related agents. Similarly, complaints that are not chronologically plausible (eg, rashes that occurred before therapy, rashes that occurred well after discontinuation of the antibiotic) can be discounted. Adverse reactions that did not recur upon subsequent exposure can safely rule out an immunologic etiology. Occurrence of known, nonimmunologic adverse reactions (eg, nephrotoxicity with aminoglycosides, red man syndrome with vancomycin) should not arbitrarily preclude future use of that antibiotic.

Finally, warnings based on cross-reactivity should be examined critically. Warnings regarding a cephalosporin are only pertinent if the inciting drug, whether penicillin or cephalosporin, shares an R group with the desired cephalosporin. Warnings regarding sulfa antibiotics should only apply if the inciting drug was a sulfa antibiotic, and should not affect use of nonantibiotics.

Even the most careful history is not definitive. Lapses in patient memory or misinterpretation of symptoms are common; therefore, the International Consensus recommends that further evaluation should occur when clinical suspicion remains, if time and local expertise permit. For those reporting a penicillin allergy, skin testing is an appropriate first step. It should use a validated protocol with nonirritating concentrations of the determinants.^{32,33} Skin testing can be considered for other antibiotics, but the procedures are much less standardized. If the skin testing is positive, then an alternative antibiotic should be used; however, if it is negative, one must still exercise some caution. Drug provocation tests, preferably orally administered, are recommended for the final verification of hypersensitivity to an antibiotic. These should be performed by trained personnel in a controlled environment to ensure safety. If significant symptoms occur, then obviously an alternative antibiotic should be chosen. If this test also yields a negative response, then the negative predictive value is >95%. In other words, the odds of reaction to that drug, although not zero, are the same as the odds of a reaction to a chemically distinct drug.

When time does not permit definitive testing initially, the prescriber must evaluate all of the potential risks and benefits based on the information at hand and, ideally, discuss the options with the patient before prescribing. If an alternative is chosen, it may be prudent to refer the patient for allergologic workup once he or she is stabilized. This can clarify the situation for future needs.

The final step with a negative workup, which also is overlooked frequently, is to update the EMR and clearly inform the patient that he or she is not allergic to the medication. This can be more difficult than one may suspect. Some EMRs do not permit deleting an allergy, but instead only allow checking a box for “resolved.” A quick glance at an allergy list may easily overlook that notation. Similarly, many EMRs do not have any fields to document the negative allergic workup. Just as we should advocate for distinct intolerance and allergy sections within EMRs and better prompting for allergic symptoms, we should advocate for more facile entry and display of data. Without it, the “allergy” can be perpetuated for some time, even after being disproven. Informing the patient may not be a simple matter either. Some patients may have reported their “allergy” for decades. They may not grasp the nuance of intolerance versus allergy and therefore it may require some time and discussion to overcome these barriers in understanding. If one fails to do this, however, then the patients themselves will perpetuate the mislabeled “allergy.”

Conclusions

Allergy warnings from an EMR present a conundrum. It is neither safe to trust them implicitly nor safe to completely

discount them. Instead, they serve primarily as a reminder to investigate their nature further. With a good history, many can be discounted. Many warnings based on cross-reactivity can be viewed as inaccurate and overridden without increased risk to the patient. Some warnings, however, may require additional evaluation. Ideally, this can be performed outside of acute situations. Once delineated, findings should be explained to patients and documented as clearly as the EMR permits. If the EMR does not permit clear documentation and updating, then it is important to advocate for improvement. Similarly, we must advocate for EMRs to eliminate warnings that are not physiologically plausible or appropriate to the patient. Although allergy warnings may never be perfect, enhancements in clinical utility are needed to improve patient safety.

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