

# LDI *Issue Brief*

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## ***Reacting to Antibiotic Allergies***

Editor's note: About 10-15% of all adults report that they are allergic to penicillin or other antibiotics, although the accuracy and significance of these reports remain unclear. In the outpatient setting, clinicians often face a dilemma in prescribing for patients with a history of an allergic reaction to antibiotics. Which drugs should these patients avoid? Are these patients at increased risk for an allergic reaction to related drugs? This Issue Brief summarizes several large studies that can help guide and improve the management of patients with antibiotic allergies.

***Antibiotic allergies are common, but the risk for subsequent allergic reactions is not known***

The discovery of antibiotics was one of the greatest medical advances of the modern era. Since the 1940s, successive classes of antibiotics have been introduced to fight bacterial infections and treat new or resistant organisms. These classes include sulfonamides ("sulfa" drugs), followed by penicillins, aminoglycosides, tetracyclines, cephalosporins, fluoroquinolones, and macrolides.

- Antibiotics are the most commonly prescribed drugs today, and the most common cause of drug-related allergies. While most allergic reactions involve mild skin irritations, some reactions can be life-threatening.
- Prescribing for a patient with an antibiotic allergy is complicated by concern over whether the patient has a related sensitivity to a different drug, a process known as "cross-reactivity." For example, patients allergic to penicillin may be allergic to cephalosporins, which have structural similarities to penicillins.
- Both overestimating and underestimating the risk of allergic reactions can harm patients. Overestimating the risk can lead to unnecessary use of more costly antibiotics or selection of less effective drugs, and may contribute to the development of drug-resistant microorganisms.

***Large-scale studies shed light on antibiotic allergies in outpatient settings***

To better understand the risk of antibiotic allergies in the outpatient setting, Strom and colleagues used the General Practice Research Database (GPRD), a large electronic database of primary care medical records and prescriptions in the United Kingdom. The GPRD contains records from nearly 700 general practitioner practices in England and Wales.

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- Using the GPRD, the researchers sought to document the nature and prevalence of allergic reactions and cross-reactivity among antibiotics. Previously, most of the evidence about antibiotic allergies had come from small studies of hospital patients, even though most antibiotics are prescribed in office settings.
  - In each study, the researchers identified “allergic-like events” in the database that occurred within 30 days after receipt of an antibiotic prescription. They used both a narrow and broad definition of these events. The narrow definition included diagnostic codes for rashes and hives, wheezing, unspecified allergic drug reactions, and more serious reactions such as anaphylaxis. The broad definition expanded the set of codes to include asthma, eczema, or an unspecified adverse drug effect.
  - One advantage of the study design is that it used diagnoses in the medical records to identify an allergic reaction, rather than relying on patient reports. It is likely that the true incidence of allergic reactions is higher than the rate ascertained by the narrow definition, and lower than the rate ascertained by the broad definition. However, the results in each study were similar using either definition, lending credibility to the findings.

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*Allergy to sulfa antibiotics may indicate a predisposition to allergic reactions to other drugs, not just to those that are sulfa-based*

Sulfa antibiotics are no longer the first-line treatment for most infections, although they are still used to treat urinary tract infections. However, non-antibiotic sulfa drugs are widely used today to treat common conditions such as hypertension, osteoarthritis, and diabetes. Clinicians have been concerned about cross-reactivity between sulfa-based drugs, and whether non-antibiotic sulfa drugs are safe for individuals with prior allergic reactions to sulfa antibiotics. To answer this question, Strom and colleagues compared allergic reactions to other sulfa drugs in those who did and did not have an allergic reaction to a sulfa antibiotic. They also examined reactions to subsequent penicillins, a biochemically distinct class of antibiotic.

- The researchers identified 20,225 patients in the database who had received a sulfa antibiotic and a subsequent non-antibiotic sulfa drug from 1987-1999. Overall, 4.8% of patients (969) had an apparent allergic reaction (using the broad definition) after receiving the initial sulfa antibiotic. Of these, 9.9% (96) had an allergic reaction after subsequently receiving a sulfa non-antibiotic. Of the patients who had no allergic reaction after a sulfa antibiotic, 315 (1.6%) had an allergic reaction after a sulfa non-antibiotic. Adjusting for other factors, patients with a history of allergies to sulfa antibiotics had nearly three times the risk of a reaction to a non-antibiotic sulfa drug as those with no such history.
  - However, when looking at patients who received a sulfa antibiotic and a subsequent a penicillin, those with a prior reaction to a sulfa antibiotic had an even greater risk of a reaction after receiving a penicillin. These patients had nearly four times the risk of a reaction to penicillin than those without a history of a reaction to a sulfa antibiotic.
  - The researchers conclude that a history of allergy to sulfa antibiotics is a marker of increased risk for allergies to subsequent drugs. This risk appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfa-based drugs.
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***Allergic reaction to penicillin is less frequent than previously thought; second prescription after an allergic-like event is common, and rarely causes problems***

Based on case studies of inpatients, the overall frequency of penicillin allergy has been reported to be about 2% per course, with the rate of recurrence upon re-exposure to penicillin as high as 60%. The rate of anaphylaxis is estimated to be 1 for every 5,000-10,000 courses of penicillin. Apter and colleagues sought to confirm these estimates in the GPRD, using the narrow definition of allergic-like events.

- The researchers identified more than three million patients who had received at least one penicillin prescription from 1987-2001. Of these, 6,212 (0.18%) experienced an allergic-like event after the initial prescription.
- Sixty per cent of all patients received a second penicillin prescription at least 60 days later. Almost half—3,014 (48.5%)—of the patients who had had an allergic reaction received a second prescription. Fifty-seven (1.9%) of these patients experienced a second reaction to the antibiotic. Few of the reactions were serious; none resulted in death. Hives accounted for about 75% of the events. Only one patient had anaphylaxis after both prescriptions.
- More than two million patients who did not have a reaction to the initial penicillin were given a second penicillin prescription. Of these, 3,452 (0.17%) patients had a reaction to the second prescription. Adjusting for other factors, patients with an initial reaction to penicillin were 9 times more likely to experience a second reaction to penicillin, although the absolute risk is small—less than 2%.
- The rate of anaphylaxis was much smaller than previously reported, and was estimated to be between 8-16 per million penicillin prescriptions.

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***Cephalosporins are not much more likely to cause allergic reactions in penicillin allergic patients than any other antibiotic***

Penicillins and cephalosporins have structural similarities, giving rise to concern about cross-reactivity. Small studies have reported that up to 10% of patients who are allergic to penicillin may experience a reaction to cephalosporins. Apter and colleagues investigated the relationship between penicillin and cephalosporin allergy in the GPRD, using the narrow definition. To distinguish cross-reactivity from a general predisposition to allergic reactions, they also investigated reactions to subsequent sulfa antibiotics.

- Of the more than three million patients receiving a penicillin prescription from 1987-2001, 534,810 received a subsequent cephalosporin at least 60 days later.
- About 1% of the 3,920 patients who had an allergic reaction after penicillin also had reaction after the cephalosporin. This is 10 times greater than the risk of a cephalosporin reaction in patients who did not have a reaction to penicillin. However, in a separate analysis of patients receiving penicillin followed by a sulfa antibiotic, patients who had a reaction following penicillin had 7 times the risk of a reaction to a sulfa antibiotic. These results suggest that cross-reactivity does not adequately explain the increased risk.
- Although the relative risk of a subsequent reaction is high, the absolute risk is very small. For example, in patients with a previous penicillin reaction, the absolute risk of anaphylaxis after a cephalosporin was less than 0.001%.

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## POLICY IMPLICATIONS

These studies provide large-scale epidemiologic evidence about antibiotic allergies as they are encountered in an outpatient setting. It sheds light on the relative and absolute risks of allergic-like events, and clarifies the risk of cross-reactivity.

- Clinicians should recognize the importance of taking a careful history about antibiotic allergies, given that prior events may be a marker for a general predisposition to allergic reactions. However, concerns about cross-reactivity between antibiotic drugs seem unwarranted. These data indicate that cephalosporins can be considered for patients with penicillin allergy, and that patients with an allergy to sulfa antibiotics do not need to be steered away from sulfa-based drugs.
- In outpatient settings, the incidence of serious reactions to penicillin (such as anaphylaxis) is much lower than previously reported, and represcription of penicillin is much more frequent than anticipated.
- However, these results must be interpreted with caution in light of the retrospective nature of the studies. Patients at risk for severe reactions may have been underrepresented, and not all of the reactions patients experienced may have been reported to their physician. Furthermore, the results apply only to outpatients given oral antibiotics; the risks associated with intravenous administration to inpatients may be much higher.
- Further research is needed to understand the mechanisms by which patients with a history of allergic reactions to antibiotics are at increased risk for subsequent reactions to unrelated compounds.

*This Issue Brief is based on the following articles: A.J. Apter, J.L. Kinman, W.B. Bilker, M. Herlim, D.J. Margolis, E. Lautenbach, S. Hennessy, B.L. Strom. Is there cross-reactivity between penicillins and cephalosporins? American Journal of Medicine, April 2006, vol. 119, pp. 354.e11-354.e20; A.J. Apter, J.L. Kinman, W.B. Bilker, M. Herlim, D.J. Margolis, E. Lautenbach, S. Hennessy, B.L. Strom. Represcription of penicillin after allergic-like events. Journal of Allergy and Clinical Immunology, April 2004, vol. 113, pp. 764-70; B.L. Strom, R. Schinnar, A.J. Apter, D.J. Margolis, E. Lautenbach, S. Hennessy, W.B. Bilker, D. Pettitt. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. New England Journal of Medicine, October 2003, vol. 349, pp. 1628-35.*

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## Issue Brief



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