

ORIGINAL ARTICLE

Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

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ABSTRACT

BACKGROUND

The safety of sulfonamide nonantibiotics is unclear in patients with prior allergic reactions to sulfonamide antibiotics.

METHODS

We conducted a retrospective cohort study using the General Practice Research Database in the United Kingdom, examining the risk of allergic reactions within 30 days after the receipt of a sulfonamide nonantibiotic. Patients with evidence of prior hypersensitivity after the receipt of a sulfonamide antibiotic were compared with those without such evidence. Similar analyses were also performed with the use of penicillins instead of sulfonamides, to determine whether any risk was specific to sulfonamide cross-reactivity.

RESULTS

Of 969 patients with an allergic reaction after a sulfonamide antibiotic, 96 (9.9 percent) had an allergic reaction after subsequently receiving a sulfonamide nonantibiotic. Of 19,257 who had no allergic reaction after a sulfonamide antibiotic, 315 (1.6 percent) had an allergic reaction after receiving a sulfonamide nonantibiotic (adjusted odds ratio, 2.8; 95 percent confidence interval, 2.1 to 3.7). However, the risk of allergic reactions was even greater after the receipt of a penicillin among patients with a prior hypersensitivity reaction to a sulfonamide antibiotic, as compared with patients with no such history (adjusted odds ratio, 3.9; 95 percent confidence interval, 3.5 to 4.3). Furthermore, among those with a prior hypersensitivity reaction after the receipt of a sulfonamide antibiotic, the risk of an allergic reaction after the subsequent receipt of a sulfonamide nonantibiotic was lower than the risk of an allergic reaction after the subsequent receipt of a penicillin (adjusted odds ratio, 0.7; 95 percent confidence interval, 0.5 to 0.9). Finally, the risk of an allergic reaction after the receipt of a sulfonamide nonantibiotic was lower among patients with a history of hypersensitivity to sulfonamide antibiotics than among patients with a history of hypersensitivity to penicillins (adjusted odds ratio, 0.6; 95 percent confidence interval, 0.5 to 0.8).

CONCLUSIONS

There is an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of a sulfonamide nonantibiotic, but this association appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.

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ANTIBIOTICS, ESPECIALLY SULFONAMIDES, are among the most common causes of allergic reactions to drugs.^{1,2} Reactions to sulfonamide antibiotics occur in approximately 3 percent of courses,^{3,4} with rashes being the most frequent type.² Sulfonamides are derivatives of sulfanilamide and contain an-SO₂NH₂ moiety.⁵⁻⁷ This moiety is also part of many common medications such as thiazide diuretics.^{5,7} Although the mechanism of sulfonamide-related reactions is poorly understood, patients who have had a reaction after taking a sulfonamide are thought to be at increased risk for another reaction,^{2,8} and all sulfonamides are considered contraindicated in those with a history of sulfa allergy.^{1,7} However, there are few data supporting this contraindication.^{1,7}

The goal of this study was to examine a prior reaction to a sulfonamide antibiotic as a risk factor for a subsequent reaction to a sulfonamide nonantibiotic. An alternative hypothesis to sulfonamide cross-reactivity is that persons with allergies to one drug are more likely to be allergic to another, even structurally unrelated, drug. To test this hypothesis, we also examined whether prior penicillin allergy was a risk factor for subsequent reaction to nonantibiotic sulfonamides.

METHODS

DATA SOURCE

A retrospective cohort study was performed with use of the General Practice Research Database, a computerized data base of medical records in the United Kingdom.⁹⁻¹¹ The data are the actual outpatient medical records from the practices of approximately 700 general practitioners and also contain

information from hospitalizations and specialist care, as recorded by the general practitioners. Established in 1987, the data base includes data on more than 8 million patients. Contributing general practitioners undergo formal training in the protocol of data entry and must demonstrate competence at entering data in the electronic data base before the data are considered "up to standard." Subsequently, each practice is subject to monthly audits to ensure that the data remain up to standard. The electronic data record includes demographic information; prescription-drug information; and indications for all new prescriptions, clinical events and diagnoses, preventive care (e.g., screening and intervention programs), hospital admissions, and cause of death; and physicians' notes about the patient. Numerous studies have used this data base,¹¹⁻¹⁴ and previous studies have suggested that the information is of high quality.^{15,16}

STUDY SUBJECTS

All patients included in the General Practice Research Database from 1987 through March 1999 were eligible for inclusion in the study if they had received a systemic sulfonamide antibiotic and had subsequently — at least 60 days later — received a prescription for a sulfonamide nonantibiotic, such as a thiazide diuretic, furosemide, or some oral hypoglycemic agents (Table 1). This was the source population from which the study and comparison groups were identified (Fig. 1). The study group consisted of those in the source population who contacted their general practitioner with a condition compatible with an allergic reaction within 30 days after receiving a sulfonamide antibiotic. The comparison group consisted of those in the source

Table 1. Sulfonamide Nonantibiotic Drugs.

Acetazolamide	Cyclopenthiiazide	Glyburide	Probenecid
Acetohexamide	Dapsone	Glymidine	Quinethazone
Bendroflumethiazide	Diazoxide	Hydrochlorothiazide	Sulfasalazine
Benzthiazide	Dichlorphenamide	Hydroflumethiazide	Sulthiame
Bumetanide	Furosemide	Indapamide	Tolazamide
Chlorothiazide	Glibornuride	Mefruside	Tolbutamide
Chlorpropamide	Gliclazide	Methyclothiazide	Torseamide
Chlorthalidone	Glimepiride	Metolazone	Xipamide
Clopamide	Glipizide	Piretanide	
Clorexolone	Gliquidone	Polythiazide	

population without evidence of such an event within 30 days after the receipt of any sulfonamide antibiotic. The outcome of interest was a contact with the general practitioner in which the diagnosis was a condition compatible with the occurrence of an allergic reaction within 30 days after the subsequent receipt of a first sulfonamide nonantibiotic. Each patient was counted only once in the analysis.

We also compared the risk of subsequent allergic reactions to penicillins among patients with and those without a prior allergic reaction after the initial receipt of a sulfonamide antibiotic. Furthermore, among those with an allergic reaction after the receipt of a sulfonamide antibiotic, we compared the risk of allergic reactions after the receipt of a subsequent sulfonamide nonantibiotic with that after the receipt of a subsequent penicillin (whichever drug was given first).

Finally, we performed an analysis of the risk of

an allergic reaction after the receipt of sulfonamide nonantibiotics, comparing patients who had had an allergic reaction after sulfonamide antibiotics with those who had had an allergic reaction after a penicillin. Patients who had received a prescription for both a sulfonamide antibiotic and a penicillin were assigned to a group according to the drug that was listed first in their medical history.

STUDY OUTCOME

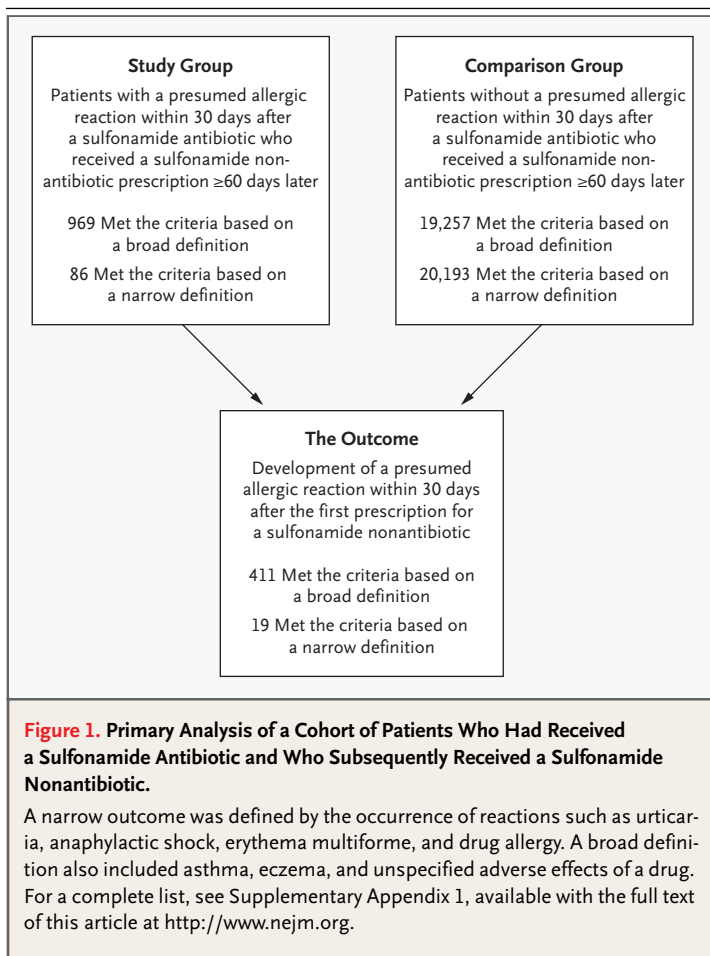
The outcome of interest was one or more codes for a hypersensitivity or allergic reaction within 30 days after receipt of the sulfonamide nonantibiotic. The analysis was completed with the use of both a narrow outcome definition (e.g., urticaria, anaphylactic shock, erythema multiforme, and drug allergy) and a broad definition, which also included asthma, eczema, and unspecified adverse effects of a drug (see Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>), since consistent results from the two analyses would help validate the choice of codes. However, we report results using the broad definition in order to avoid missing a substantial number of outcomes and because it provides more statistical precision and the ability to control for confounding.

Outcomes occurring on the same day as the prescription for the sulfa drugs were not included because these may have preceded or even have been the indication for the treatment. The results did not substantively change, however, whether or not these data were included (data not shown).

STATISTICAL ANALYSIS

After descriptive analyses, we calculated unadjusted odds ratios and associated 95 percent confidence intervals. Since the outcome under investigation in this study is a rare event, the odds ratio is a close estimate of the relative risk. We then calculated adjusted odds ratios and 95 percent confidence intervals using logistic regression,¹⁷ controlling for multiple potential confounders one at a time (see Supplementary Appendix 2, available with the full text of this article at <http://www.nejm.org>). Next, we controlled simultaneously for all confounders that changed the point estimate of the odds ratio by 15 percent or more.¹⁸⁻²⁰ We also tested for interactions between the study group and each confounder.

Subanalyses to identify high-risk subgroups were performed according to the age at the time of the outcome (<65 years vs. ≥65 years), for pa-



tients using only trimethoprim–sulfamethoxazole, and for four categories of sulfonamide nonantibiotic agents, which were grouped according to their relative degree of similarity to the structure of the sulfonamide antibiotic: thiazides only, loop diuretics only, sulfonamide only, and other sulfonamide nonantibiotic agents. We repeated analyses, separately examining the risk of specific types of reactions.

Finally, we repeated the unadjusted analysis using cessation of therapy as the outcome (i.e., discontinuing the long-term use of the sulfonamide nonantibiotic drug) instead of hypersensitivity or allergic reactions, to preclude missing any reactions that were not coded but simply led to discontinuation of these usually long-term therapies.

Analyses used SAS software, version 8.0.²¹ The study was approved by the General Practice Research Database Scientific and Ethical Advisory Group of the Medicines Control Agency in the United Kingdom and the University of Pennsylvania Committee on Studies Involving Human Beings. The academic investigators were responsible for all aspects of the study, including writing the protocol, obtaining and processing the data, performing all analyses and statistical analyses, and drafting the manuscript. The industry-based investigator reviewed all of the above and provided important substantive suggestions at the first and last level, including suggesting the supplementary analyses. The final content of the manuscript was controlled by the academic investigators, with no restrictions.

RESULTS

Overall, 4.8 percent of patients (969 of 20,226) had an apparent allergic reaction within 30 days after receiving the initial sulfonamide antibiotic with use of the broad definition, and 0.4 percent (86 of 20,279) had an allergic reaction with use of the narrow definition. (These denominators differ slightly, because we excluded more patients with prior disease using the broad definition than using the narrow definition.) In both groups, 67.5 percent of patients were female and 43.5 percent of patients were 65 years of age or older at the time of exposure.

Overall, 2.0 percent of patients (411 of 20,301) had an apparent allergic reaction after subsequently receiving a sulfonamide nonantibiotic with use of the broad definition, and 0.1 percent (19 of 20,391) did so with use of the narrow definition. Patients with prior hypersensitivity after sulfonamide anti-

biotics and those without such a history were similar with respect to age ($P=0.24$), sex ($P=0.94$), and duration of follow-up in the General Practice Research Database ($P=0.62$).

A total of 9.7 percent of allergic reactions after the sulfonamide nonantibiotics (40 of 411) were serious enough to require hospitalization. The most common diagnoses included in our composite end point were asthma (288 of 411, or 70.1 percent), eczema (58 of 411, or 14.1 percent), and adverse drug reactions (47 of 411, or 11.4 percent). With the use of our narrow definition of outcome, the comparative results were not substantively different. Therefore, we used the broad definition for all subsequently presented results, unless specified otherwise.

The unadjusted odds ratio for the association between hypersensitivity or allergic reactions after receipt of a sulfonamide nonantibiotic and a history of hypersensitivity or allergic reactions to sulfonamide antibiotics, as compared with no such history, was 6.6 (95 percent confidence interval, 5.2 to 8.4) with use of the broad definition (Table 2) and 13.2 (95 percent confidence interval, 1.7 to 99.9) with use of the narrow definition. Results that included only the subgroup of patients whose symptoms were consistent with those of type I hypersensitivity or IgE-mediated reaction (i.e., anaphylaxis, bronchospasm, urticaria, laryngospasm, or angioedema) were substantively the same but imprecise, since only 18 patients had such reactions.

Since the majority of patients (98.4 percent) received trimethoprim–sulfamethoxazole as the initial drug, the results were identical between the group as a whole and the subgroup of patients who received trimethoprim–sulfamethoxazole as their initial sulfonamide antibiotic. The results also did not change substantively when the subgroups were classified according to the subsequent sulfonamide nonantibiotic that was prescribed: the unadjusted odds ratio was 5.7 (95 percent confidence interval, 4.0 to 8.3) for thiazides alone, 7.0 (95 percent confidence interval, 5.1 to 9.3) for loop diuretics alone, 6.9 (95 percent confidence interval, 3.0 to 15.9) for sulfonamide only, and 3.6 (95 percent confidence interval, 0.2 to 72.3) for other sulfonamide nonantibiotics.

Of the large number of potential confounders investigated, we found that the only variables that changed the odds ratio by at least 15 percent were preexisting asthma and prior use of asthma medications and corticosteroids. The adjusted odds ratio

Table 2. Summary Results of Primary and Supplemental Analyses.*

Outcome	Patients with Prior Hypersensitivity after Sulfonamide Antibiotics	Patients without Prior Hypersensitivity after Sulfonamide Antibiotics	Unadjusted Odds Ratio (95% CI)	Odds Ratio Adjusted for 5 Variables (95% CI)†	Odds Ratio Adjusted for 18 Variables (95% CI)‡
	no./total no. (%)				
Allergic reaction within 30 days after receipt of a sulfonamide nonantibiotic	96/969 (9.9)	315/19,257 (1.6)	6.6 (5.2–8.4)	2.8 (2.1–3.7)	2.8 (2.1–3.7)
Allergic reaction within 30 days after receipt of a penicillin	717/5115 (14.0)	2307/112,935 (2.0)	7.8 (7.1–8.5)	3.9 (3.5–4.3)	3.8 (3.4–4.2)
Allergic reaction within 30 days after receipt of a sulfonamide nonantibiotic	65/631 (10.3)	—§	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.5–0.9)
Allergic reaction within 30 days after receipt of a sulfonamide nonantibiotic	81/889 (9.1)	—¶	0.6 (0.4–0.7)	0.6 (0.5–0.8)	0.6 (0.5–0.8)

* CI denotes confidence interval.

† The odds ratios were adjusted for sex, age at outcome, and the presence or absence of a history (i.e., before receipt of the index sulfonamide antibiotic) of asthma, use of drugs for asthma, and use of corticosteroids.

‡ The odds ratios were adjusted for the five variables as well as for the presence or absence of a history of eczema, hay fever, allergic rhinitis, urticaria, sinusitis, cellulitis, adverse drug reactions, urinary tract infection, systemic lupus erythematosus, rheumatoid arthritis, other connective-tissue diseases, use of antihistamines, and use of anticonvulsants.

§ Among 4982 patients with a history of hypersensitivity after the receipt of penicillin (the comparison group), 707 (14.2 percent) had an allergic reaction within 30 days after the receipt of a penicillin.

¶ Among 4736 patients with a history of hypersensitivity after the receipt of penicillin (the comparison group), 693 (14.6 percent) had an allergic reaction within 30 days after the receipt of a sulfonamide nonantibiotic.

(after controlling for sex, age at outcome, and the presence or absence of preexisting asthma, prior use of asthma medications, and prior use of corticosteroids) was 2.8 (95 percent confidence interval, 2.1 to 3.7). The odds ratio was 2.9 (95 percent confidence interval, 1.9 to 4.2) for those younger than 65 years old and 2.6 (95 percent confidence interval, 1.7 to 4.0) for those 65 years of age or older. With the use of cessation of the sulfonamide nonantibiotic therapy (instead of allergic reactions) as the outcome, prior hypersensitivity to sulfonamide antibiotics was not a predictor for stopping therapy with a sulfonamide nonantibiotic (unadjusted odds ratio, 1.1; 95 percent confidence interval, 0.9 to 1.2).

Finally, to place the above results in perspective (Table 2), the unadjusted odds ratio for an allergic reaction after the receipt of a prescription for a penicillin for those with a prior reaction after a sulfonamide antibiotic, as compared with those without such a reaction, was 7.8 (95 percent confidence interval, 7.1 to 8.5), with an adjusted odds ratio of 3.9 (95 percent confidence interval, 3.5 to 4.3). Among those with an allergic reaction after receiving a sulfonamide antibiotic, the unadjusted odds ratio for an allergic reaction to a subsequent sulfonamide

nonantibiotic, as compared with a subsequent penicillin, was 0.7 (95 percent confidence interval, 0.5 to 0.9), and the adjusted odds ratio was 0.7 (95 percent confidence interval, 0.5 to 0.9). Indeed, comparing patients with prior evidence of hypersensitivity after sulfonamide antibiotics with patients with prior evidence of hypersensitivity after penicillins showed that an allergic reaction occurred in 9.1 percent (81 of 889) and 14.6 percent (693 of 4736), respectively, within 30 days after they had received a subsequent sulfonamide nonantibiotic drug (unadjusted odds ratio, 0.6 [95 percent confidence interval, 0.4 to 0.7]; adjusted odds ratio, 0.6 [95 percent confidence interval, 0.5 to 0.8]) (Table 2).

DISCUSSION

Our results suggest that, although allergy to a sulfonamide antibiotic is indeed a risk factor for a subsequent allergic reaction to a sulfonamide nonantibiotic, a history of penicillin allergy is at least as strong a risk factor. The association initially seen in the primary analysis with the sulfonamide nonantibiotics might be explainable by a general predisposition to allergic reactions among certain patients

rather than a specific cross-reactivity with drugs containing the sulfa moiety. Thus, our results suggest that, if sulfonamide-based nonantibiotics were to be avoided in those with a prior sulfa allergy, they would also have to be avoided in those with a prior penicillin allergy. Alternatively, and perhaps more rationally, prescribers should simply understand that patients with a history of any type of allergic reaction after the receipt of sulfonamides or penicillins may be at increased risk for reactions to other drugs, rather than consider sulfonamides a specific contraindication. Indeed, previous data have indicated that a history of an adverse drug reaction increases the risk of a subsequent adverse drug reaction.^{1,22} Some data suggest that persons with atopy are at higher risk for reactions to penicillin,²³ radiocontrast dye,^{24,25} anesthetics,²² muscle relaxants,²² barbiturates,²² acetaminophen,²⁶ nonsteroidal antiinflammatory drugs,²⁷ and multiple antibiotics.²⁸ Other data indicate that persons with atopy are not at increased risk for a drug hypersensitivity reaction,^{1,29,30} but that they may have more severe reactions.^{1,22,31}

Although sulfonamide allergy is unpredictable and potentially life-threatening, there are few systematic investigations of these reactions and even fewer studies of the risk of hypersensitivity reactions after the subsequent receipt of a nonantibiotic sulfonamide. Understanding these risks is especially important, because sulfonamide allergy is common. In addition, sulfonamide nonantibiotics include members of many extremely important pharmacologic classes. Previous data indicating a link between an allergic reaction to a sulfonamide nonantibiotic and a history of a reaction to a sulfonamide antibiotic are limited primarily to case reports.^{6,32-34} One meta-analysis of data from clinical trials of celecoxib, an antiinflammatory agent containing an arylsulfonamide moiety, found no increased risk of an allergic reaction related to sulfonamide sensitivity.⁶ A small cohort study at two teaching hospitals did not find cross-reactivity between trimethoprim-sulfamethoxazole and dapsone.³⁵ We used a much larger cohort to explore systematically the risk of allergic reactions to all sulfonamide nonantibiotics in patients with a history of sulfonamide allergy. However, we could not include data on the use of some newer drugs, including celecoxib. Because allergens, haptens, and other immune mechanisms for sulfonamide hypersensitivity have not been identified, this risk could not be studied with the use of immunologic methods.

Several limitations may have influenced our results. Information bias could have resulted if the two study groups were asymmetric with respect to the completeness of the information on outcomes. However, the assessment of outcome was not dependent on the patients' recall or on interviewers, since the information was obtained from computerized medical records. Furthermore, we did not rely on physicians' attribution of adverse drug reactions. Although there are codes in the General Practice Research Database for drug-induced disease, we have no way of ensuring that the general practitioners used such a code rather than a code for the outcome itself (e.g., urticaria). Therefore, we were hesitant to make such a distinction. In addition, the validity of the attributed link in such case reports is questionable in many instances, because a clinician cannot always determine whether urticaria is due to a patient's exposure to a sulfonamide antibiotic, is related to another precipitant, or is idiopathic. The uncertain validity of such subjective judgments is why comparative epidemiologic studies such as ours are needed.

So-called diagnostic suspicion bias could have occurred if patients who had the exposure of interest were more closely monitored for the outcome of interest than those without this exposure; that is, if physicians were more likely to monitor patients with a history of sulfa allergies for allergic reactions after administering a nonantibiotic sulfonamide. However, such bias would have increased the risk of a positive association in the comparison of sulfonamides with penicillins, in contrast to the inverse association that we found.

Outcome misclassification might have occurred if the outcomes did not come to medical attention. However, they would have been detected in our analyses in which cessation of sulfonamide nonantibiotics was the outcome variable. Outcome misclassification could also have occurred if physicians did not use a formal diagnosis to document milder outpatient drug reactions, such as maculopapular rashes. Since we relied on primary medical records, not on claims data, this possibility is less likely to have been a problem. In addition, there is no reason why this factor should have differed between the study groups. Outcome misclassification could also have occurred if a patient had chronic allergic symptoms (e.g., asthma) and coincidentally took a sulfonamide. However, we controlled for preexisting allergic reactions in the analysis.

A selection bias might be introduced from the

loss of patients after enrollment (either due to death or to transfer out of the practice). Such a loss is unlikely in a medical-record data base of general practitioners in the United Kingdom and was unlikely to be unequal in the two study groups.

Selection bias could also have been introduced if a patient with a prior sulfonamide antibiotic reaction were less likely to be prescribed a nonantibiotic sulfonamide than a patient with no such history. However, when we compared those with an allergic reaction within 30 days after receipt of the initial sulfonamide antibiotic with those without such a reaction, examining the probability of being prescribed a subsequent sulfonamide nonantibiotic at least 60 days later, we found a relative risk of 1.13 (95 percent confidence interval, 1.06 to 1.21). In other words, those with an allergic reaction after a sulfonamide antibiotic were slightly more likely to receive a subsequent sulfonamide nonantibiotic than those without such a history (17.0 percent vs. 15.3 percent). It is possible, however, that those with certain types of initial reactions were preferentially steered away from subsequent exposures. However, our results did not differ substantively according to whether the initial reaction did or did not meet our strict definition or whether the initial reaction did or did not result in hospitalization.

Thus, it seems very unlikely that such a selection process could have affected our results.

Finally, we controlled for a large number of potential confounders in the analyses, and substantial confounding was seen from preexisting asthma and its treatment, which can, of course, be related both to subsequent asthma and to the use of antibiotics and other medications. We also cannot be certain that there were no other variables for which we could not control.

Thus, although a history of allergy to sulfonamide antibiotics is a marker of increased risk on subsequent exposure to sulfonamide nonantibiotics, our results suggest that this risk is not unique to sulfonamide antibiotics. Indeed, patients with a history of hypersensitivity to sulfonamide antibiotics are at even greater risk for subsequent reactions to penicillins, a biochemically distinct group, than to nonantibiotic sulfonamides. Prescribers should understand that patients with a history of allergic reactions to drugs may be at increased risk for all drug-induced adverse events that appear to be allergic in nature.

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