

Risk factors for drug allergy

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Judging from available data on penicillin allergy there appear to be multiple definable risk factors for drug-induced immunopathology. The induction of a drug-specific immune response can be influenced by the age of the patient; underlying genetic or metabolic factors, which may restrict ability to initiate a drug-specific immune response; the chemical properties of the drug, largely its protein reactivity; and the dose and duration of treatment as well as the route of drug administration. The elicitation of drug-induced immunopathology is a function of the persistence of a drug-specific immune response; the frequency of drug treatment and its dose and duration; and probable constitutional factors that may determine in an important way the efficiency with which a drug-specific immune response can be translated into a systemic allergic reaction. (J ALLERGY CLIN IMMUNOL 74:567, 1984.)

Even with highly sensitizing drugs, only a small percentage of patients with multiple drug exposures develop adverse reactions that can be attributed to a drug-specific immune response. In a large population of clinic patients with sexually transmitted disease in Baltimore, we have prospectively observed more than 8000 patients for evidence of allergic reactions after penicillin treatment. In that setting we found an incidence of posttreatment "allergic" reactions of only 1.45% among unselected patients without histories of prior penicillin allergy. What factors contribute to the risk of these unusual allergic reactions to drugs? This article attempts to address this clinically important question. Most of what we know regarding risk factors for drug allergy has been derived from studies of allergy to the penicillin group of drugs—far and away the most prevalent cause of allergic drug reactions. The principles involved in penicillin allergy will hopefully be applicable to other allergenic drugs as well.

Some influences worthy of consideration are listed in Table I. It is useful to separate, insofar as possible, effects on the induction of a drug-specific immune response from those contributing to the elicitation of a clinically overt reaction in a previously sensitized subject. The table indicates my rather crude assessment of the likelihood that each of seven factors will influence the induction or elicitation phases of drug allergy. The terms "likely" and "unlikely" have been

chosen rather than the more concrete "yes" or "no" to emphasize the fact that in almost all cases the conclusions to be drawn are soft and are drawn from limited data and often indirect observations. Unfortunately few attempts have been made to definitively assess the quantitative effects of the patient and treatment variables about to be discussed.

A good illustration of this point is the first relevant patient factor—age. Age is judged "likely" to exert a significant influence on the induction of drug allergy largely because of two clinical observations. First, it is generally agreed (without much firm supportive data) that pediatric populations suffer fewer allergic reactions to penicillin than adults who receive comparable doses.¹ Younger age is likely to be associated with less cumulative drug exposure, and the contribution of this factor has not been sorted out. Second, there is evidence from studies of Hymenoptera allergy that immunoglobulin (Ig) E antibody responses in children, as assessed by skin or radioallergosorbent tests, dissipate more rapidly than those of adults.² This may be true for drug-specific IgE as well, although one cross-sectional analysis did not support this notion.³ There are unfortunately no prospective studies in children of the prevalence of penicilloyl IgE antibody responses or their rate of disappearance.

Similarly, age is judged "unlikely" to have a major effect on the elicitation of drug allergy solely on the grounds that severe drug-induced immunopathology can and does occur in small children. After the neonatal period, there is little evidence to suggest that children lack any of the mechanisms of immunopathology observed in adults. The possibility of a quantitative distinction remains. This is clearly an area

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TABLE I. Personal and treatment factors contributing to drug-induced immunopathology

	Influence on	
	Induction of drug-specific immune response	Elicitation of clinically overt reaction
<i>Personal factors</i>		
1. Age	Likely	Unlikely
2. Genetic/constitutional factors		
a. Specific immune responsiveness	Likely	—
b. Atopy (re: IgE mediation)	Unlikely	Likely
3. Persistence of immune response	—	Likely
<i>Treatment factors</i>		
1. Chemical properties of drug	Likely	Likely
2. Dose, duration of treatment	Likely	Likely
3. Route of drug administration	Likely	Not clear
4. Frequency of drug treatment	Unlikely	Likely

where additional age-related research is needed, not only with regard to the genesis of drug allergy, but concerning the expression of immunopathologic reactions in general.

Several constitutional or genetic factors are likely to be important determinants of drug allergy. Experimental studies in animals have indicated a genetic basis for the ability to respond immunologically to a variety of haptens and low-molecular-weight polymers.⁴⁻⁶ To pursue this hypothesis in man, we have studied the IgG and IgE antibody responses after administration of penicillin to 60 hospitalized patients who received at least 2 gm for 10 or more days. The antibody response specific for the major penicilloyl determinant was determined serologically.⁷⁻⁹ Eighteen percent of the patients made IgG alone, 20% made both IgG and IgE, but a majority mounted no detectable serologic response. These data suggest that only about half of the adult population can respond to penicillin administration with a detectable IgG or IgE antibody response. There are of course numerous possible explanations for apparent nonresponsiveness to high-dose penicillin administration.¹⁰ Whatever the ultimate explanation, however, it is reasonable to expect that nonresponders will have substantially reduced risk of not only IgE-mediated allergy but other immunologic reactions to penicillin as well.

Another genetic constellation worthy of consideration with regard to IgE-dependent drug reactions is the constitutional diathesis that has traditionally been called "atopy." The atopic disposition carries with it a higher than expected incidence of allergic rhinitis, allergic asthma (usually with onset in childhood), and/

or atopic dermatitis. A useful marker of the atopic state is an elevated total serum IgE.¹¹

There are two lines of evidence to support the assertion that atopy has little effect on the *induction* of a drug-specific IgE response. First, we did not observe any difference in the total serum IgE levels of the IgE responders and nonresponders in the study of penicilloyl immune responsiveness mentioned above.* The second observation pertinent to this point concerns the rates of clinically assessed atopy as indicated by responses to questions regarding prior history of seasonal rhinitis, allergic asthma, or atopic dermatitis among 4069 patients who were skin tested for penicillin allergy. All patients had negative histories of penicillin allergy and were skin tested with penicilloyl polylysine and a minor determinant penicillin mixture. Use of these two reagents is thought to be sufficient to detect most of the clinically important IgE antibody responses to penicillin antigens.^{3, 12-16} The results indicate that there is no difference in the frequency of atopy by history in skin test-positive as opposed to skin test-negative subjects (Fig. 1). These findings are compatible with the suggestion that an atopic background does *not* predispose to a higher rate of drug-specific IgE antibody responses.

On the other hand, an atopic background is found with a high frequency among patients suffering severe and fatal anaphylactic reactions.^{17, 18} It even appears that atopic individuals are at greater risk for serious pseudoallergic reactions such as those to contrast media where IgE-dependent mechanisms are not in-

*Adkinson NF, Wheeler B: Unpublished data.

TABLE II. IgE-dependent reactions among patients with negative penicillin skin tests

History of prior reaction	Rate of IgE-dependent reactions after treatment* (%)
Anaphylaxis	15.4 [†] (2/13)
Urticaria	7.8 [‡] (15/192)
Exanthem	2.4 [§] (3/126)
Other/uncertain	0.5 (1/202)
None	0.45 (18/3996)

*During first 72 hours of treatment. Of the 21 reactions among history-positive patients, 16 involved transient urticarial reactions, three cases included angioedema, and three cases manifested mild dyspnea and/or dysphagia. There were no cardiovascular alterations in any case.

[†] $p = 0.002$.

[‡] $p < 0.0001$.

[§] $p = 0.049$.

involved.¹⁹ Whatever its basis, the atopic constitution appears to carry with it a substantially increased risk of serious allergic reactions once an IgE antibody response has been mounted.

Genetic or constitutional factors other than atopy may also play a role in the elicitation of IgE-dependent reactions. We have recently obtained data that support the concept that a conglomeration of patient factors relating to an individual's ability to translate an IgE antibody response into a clinically manifested allergic reaction may constitute an important risk factor. As part of a prospective, randomized study of penicillin skin testing, we treated and observed for reaction 3996 patients with negative histories of prior penicillin reactivity and negative penicillin skin tests. Among these patients, 18 had reactions within the first 72 hours of therapy that were judged on clinical grounds to be probably IgE mediated. This translates to an IgE-dependent reaction rate of 0.45% among history-negative, skin test-negative subjects. In the same clinical population, we also skin tested and treated 533 individuals with histories of prior penicillin reactions, but whose penicillin skin tests were currently shown to be unambiguously negative. The observed 72-hour reactions rates for probable IgE-mediated reactions are as shown in Table II. The important observation here is that the rates for probable IgE-mediated reactions were significantly higher among patients with histories of urticaria and anaphylaxis than among patients with histories of other penicillin allergy or with negative histories.

It is important to recall that all of the patients in the first two categories had previously sustained prob-

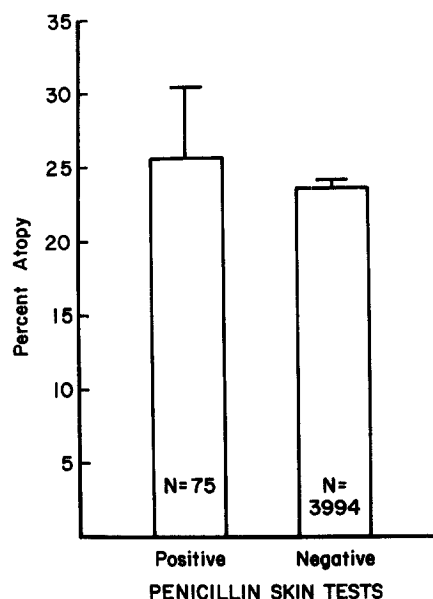


FIG. 1. Frequency of atopy among 4069 subjects skin tested for penicillin allergy. Subjects were randomly selected from clinic patients with sexually transmitted disease who required penicillin therapy for an active infection. All subjects denied prior penicillin reaction. Atopy was determined by any positive response to questions regarding personal history of allergic asthma, seasonal rhinitis, and/or atopic dermatitis. The rate of atopy did not differ between skin test-positive and skin test-negative subjects ($p = 0.78$; Fisher's exact test).

able IgE-mediated reactions and had unequivocally negative penicillin skin tests prior to their treatment. Hence, their reactions must be presumed due to very small amounts of IgE antibodies that are undetectable by standard skin testing techniques. While such a small amount of drug-specific antibody may be of no clinical consequence for most patients, it appears to be capable of mediating urticarial and anaphylactic reactions more readily in patients who have sustained such reactions in the past. It may be that some or all of these reactions in skin test-negative patients are not IgE dependent, but are pseudoallergic or idiosyncratic in origin. Nevertheless, the fact remains that patients who previously sustained anaphylactic or urticarial reactions to penicillin are at greater risk for recurrence of such reactions if they are retreated—even when IgE antibodies are undetectable by skin testing. The relationship of *this* constitutional risk factor to atopy, as classically defined, remains to be determined.

A third factor that clearly influences the cumulative risk of penicillin allergy is the persistence of drug-specific antibodies once they are formed. We are conducting an ongoing study to assess prospectively the

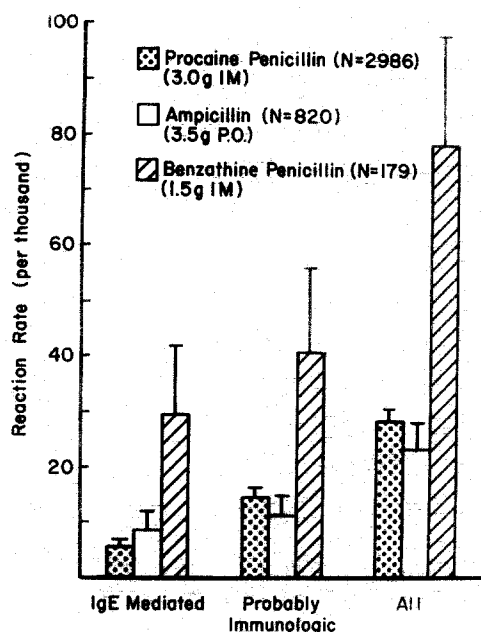


FIG. 2. Comparison of reaction rates for three penicillin treatment regimens. All subjects gave negative histories of prior penicillin reactions; none were skin tested prior to treatment. Treatment regimens were chosen on clinical grounds, independently of study. Reactions within 72 hours of initiation of treatment were designated on clinical criteria to be IgE mediated (urticaria, anaphylaxis). The "probably immunologic" category included IgE-mediated reactions, plus pruritus and/or nonurticarial skin eruptions. The "all" category included reactions of any type attributed by the patient to penicillin treatment. In all three categories, the reaction rates for oral ampicillin and procaine penicillin did not differ by chi-square analysis ($p = 0.23$ to 0.89), while that for benzathine penicillin was significantly higher ($p = 0.003$ to 0.01).

natural history of penicillin allergy in man. This involves the periodic longitudinal follow-up of patients who have positive penicillin skin tests. More than 50 such patients are currently being evaluated with routine penicillin skin tests and serologic determinations of penicilloyl IgG and IgE antibodies every 6 to 8 weeks. Although the study is incomplete, available data indicate that the penicilloyl IgE antibody half-life in serum ranges from as short as 10 days to an indeterminately long interval (>1000 days). The rate of decline of penicillin antibodies cannot as yet be related to any clinical or immunologic parameters, including the recentness of penicillin therapy, antibody titer at entry, or the patient's history of prior penicillin reaction. Furthermore, the half-life of penicilloyl IgE antibody is not significantly correlated with the half-life of IgE tetanus antibody in the same patients. This finding suggests that the persistence of penicilloyl IgE antibodies depends on some factors

that are independent of those controlling the metabolism of IgE antibodies in general. Further study will be needed to determine what these host factors are and the role, if any, of occult exposure to penicillin or cross-reacting antigens in the environment. It is obvious, however, that whatever the reason, the persistence of IgE antibody over long periods of time carries with it a cumulative risk of penicillin allergy much greater than that experienced by patients whose drug-specific antibody levels decline rapidly.

There are at least four treatment-related factors that may influence the rate of induction and/or elicitation of allergic drug reactions. The first of these is the chemical properties of the drug. We now know quite conclusively from multiple lines of evidence that this is a pivotal determinant of drug allergies, with a strong influence on both the induction of a drug-specific immune response and the subsequent elicitation of immunopathology. In work by Herman Eisen²⁰ and his colleagues in the early 1950s, the rate of contact sensitization by simple chemicals was found to be directly related to the rate of conjugation of those chemicals to large-molecular-weight carriers, usually proteins. This concept has now achieved the status of immunologic dogma. In general this principle has been borne out clinically. Highly allergenic drugs invariably have significant protein reactivity, and those drugs that are relatively inert with regard to protein interactions enjoy a very low incidence of allergic side effects.^{21, 22}

The numerous ways in which penicillin can interact covalently with proteins has been well worked out thanks to a decade of pioneering work by Drs. Charles Parker and Bernard Levine and their associates.²³⁻²⁶ It should be pointed out that the covalent attachment of penicillin to proteins occurs at a measurable rate under physiologic conditions without the need for enzymes or cofactors.^{27, 28} Hence, it is possible to detect penicilloated proteins in the serum of nearly every patient receiving moderate doses of penicillin drugs.* Thus the failure to observe a penicilloyl immune response in a patient on long-term penicillin therapy is *not* likely to be explained by the patient's inability to produce drug protein conjugates. This situation with penicillin stands in contrast to that of other drugs such as isoniazid and hydralazine where a genetically determined capacity to acetylate the drug may contribute to its immunogenicity in some patients.^{22, 29}

The dose and duration of drug treatment are likely, within limits, to affect the induction of a drug-specific immune response. Evidence of this comes largely

*Adkinson NF, Wheeler B: Unpublished data.

from studies in experimental animals. The dose and duration of drug treatment may also influence the elicitation of immunopathology. For example, drug-induced cytopenias, interstitial nephritis, and serum sickness reactions occur more frequently with higher-dose, longer-term therapy.³⁰⁻³² Even IgE-dependent reactions are dose related; anecdotal cases are reported in which patients tolerate a given level of treatment, but manifest acute allergic reactions when the dose is increased.³³ Furthermore, the duration of treatment defines the temporal period of risk and thereby influences immunopathology independent of any effect it may have on immune responsiveness.

Another risk factor is the route of drug administration. Regarding the *induction* phase, the use of topical penicillin has been largely abandoned due in large part to the high rate of contact sensitization observed during its early use in toothpastes and mouthwashes in Europe.¹⁷ Otherwise there is little evidence that the risk of sensitization is greater for one route of treatment than for another.

Two clinical surveys have found that penicillin reactions were elicited almost twice as often with parenteral administration as with oral administration.^{34, 35} In reviewing the world literature, Sullivan et al.³³ noted that each year only six anaphylactic deaths occurred after oral administration of β -lactam drugs compared to hundreds of penicillin-induced fatalities after parenteral administration. However, our recent experience suggests that with careful follow-up, reaction rates for *similar doses* of oral and parenteral penicillin may be comparable.

Fig. 2 shows results from a prospective treatment protocol in which three treatment regimens were compared: procaine penicillin, 3 gm intramuscularly; ampicillin, 3.5 gm orally as a single dose; and benzathine penicillin, 1.5 gm intramuscularly. One gram of probenecid was given orally along with the parenteral procaine penicillin and the oral ampicillin. Reactions occurring within 72 hours of penicillin treatment were documented. Results are similar for all reported reactions, those judged of probable immunologic origin and those judged clinically to be likely IgE mediated. In each case there is no difference in the reaction rate observed with comparable doses of procaine penicillin and orally administered ampicillin. The reaction rates for benzathine penicillin were significantly higher, despite its lower dose, suggesting that the benzathine additive is responsible for the excess reaction rate. This finding of a higher reaction rate for benzathine penicillin and other depo-type penicillins is in agreement with other available studies.³⁶

This failure to demonstrate an increased reaction

rate for intramuscular procaine penicillin could be due to the excess rate of reactions associated with ampicillin as opposed to benzylpenicillin, or to the use of probenecid to boost serum levels. Nevertheless, these results raise the question of whether the reported differences in reaction rates for oral versus parenteral penicillin may not be due more likely to a difference in usual dose than the route of administration.

Finally, there is little evidence that the frequency of drug treatment affects the likelihood of sensitization. On the other hand, the frequency of drug usage has a marked influence on the likelihood of *eliciting* an allergic reaction. In the case of IgE-dependent penicillin allergy, most patients lose their IgE antibody and hence their sensitivity over a finite period of time.^{3, 10, 12, 14} Thus, the more frequently the drug is administered, the more likely that an IgE-dependent reaction will be provoked. By analogy, this may also apply to other forms of drug-induced immunopathology.

It should be clear from the tentative nature of all of the conclusions drawn that much important work has yet to be undertaken. In considering future research directions, an emphasis on *patient*-related variables rather than the treatment-related factors is to be desired. This is because drug allergy is rare enough that treatment-related risk factors are *unlikely* to have a significant impact on the way we use drugs clinically—that is, on the dose, duration, route, and frequency of prescribed drug therapy. An exception to this generalization would be knowledge of the chemical properties of a drug, particularly its protein reactivity, since such information may impact on drug design and premarket estimates of allergenic potential. On the other hand, patient-related factors are of immense practical importance since they may identify individuals who have generally increased risk for multiple allergic drug reactions or for multiple types of immunopathology. In the case of penicillin allergy, for example, if high-risk patient subsets can be identified, then routine penicillin skin testing before treatment can be made vastly more cost-effective.

Since drug-specific immune responses occur much more frequently than drug-induced immunopathology, attention should be focused on the patient factors that are responsible for translating a drug-specific immune response into an allergic reaction. These factors need to be delineated and quantified. As concerns drugs whose prevalence of use or reaction rates are less than for β -lactam antibiotics, *collaborative* research efforts involving laboratory, clinical, and epidemiologic studies will be necessary for findings to be conclusive. Such studies are likely to be successful only if un-

dertaken as a joint venture involving interested investigators, federal agencies, and the pharmaceutical industry.

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