

Controversies in Allergy: Is Skin Testing Required Prior to Drug Challenges?



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INTRODUCTION

At the American Academy of Allergy, Asthma, and Immunology (AAAAI) 2018 Annual Meeting in Orlando, Florida, the following issue was debated: “Skin testing is required prior to drug challenges.” The pro position was presented by Luis Felipe Ensina. The con position was presented by Eric Macy. Each position considered the existing data on the safety of drug hypersensitivity evaluations done with and without skin testing. The present article is an account of the pro/con debate and does not constitute a systematic review of the literature.

THE PRO POSITION—DR ENSINA

Drug hypersensitivity affects more than 7% of the population.¹ An incorrect diagnosis may limit therapeutic options and lead to the use of more expensive and potentially less effective drugs. As a confirmed drug hypersensitivity reaction (DHR) occurs in less than 50% of patients with suggestive history, a complete diagnostic workup is recommended.² The investigation of DHR should be based on the mechanism of the reaction, implicated drugs, and severity of presenting symptoms.¹

DHRs can be classified as immunologically mediated or non-immunologically mediated. Immunologically mediated hypersensitivity can occur when drug- or drug-metabolite-specific IgE or T cells are produced. Acute-onset urticaria, angioedema, and anaphylaxis are examples of IgE-mediated hypersensitivity reactions, whereas delayed-onset maculopapular rashes, fixed drug eruptions, and severe cutaneous adverse reactions (SCARs) are examples of T-cell-mediated hypersensitivity. For both types of reactions, *in vitro* and *in vivo* diagnostic testing can be useful.¹

In nonallergic DHR, inflammatory mediators are released by antigen-nonspecific mechanisms, such as direct mast cell activation associated with multiple nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapies, and iodinated radiocontrast media. These reactions frequently present as acute-onset urticaria, angioedema, or anaphylaxis, but skin or *in vitro* tests are often not indicated, as there is no antigen-specific mechanism involved.³ Conformation for non-immune-mediated DHR is typically limited to the drug provocation test (DPT).⁴

In theory, any drug can induce a DHR. However, knowing and understanding the association of each class of drug with a specific type of reaction may help us to choose the adequate method of investigation. For example, acute-onset urticaria that follows amoxicillin treatment potentially has an IgE-mediated mechanism and its assessment could include measuring amoxicillin-specific serum IgE levels and/or skin prick and intradermal testing. On the other hand, an NSAID-induced urticaria is frequently related to a cyclooxygenase-1 inhibition mechanism, and its investigation should be limited to a DPT.⁵

It is recommended that drug allergy investigation be performed at least 4 to 6 weeks after complete resolution of symptoms and signs, but ideally not more than 6 to 12 months when the drug tests may have already turned negative.¹ Clinical history is the first approach for diagnosis, but it is often unreliable leading to an incorrect diagnosis. The DPT is considered the reference standard for diagnosing DHR or confirming current tolerance. Nevertheless, it can be time consuming and can often only be performed in a specialized center by trained personnel, as it may mimic in severity the original reaction.⁴

In vitro tests are safe for both immediate and nonimmediate reactions, as the patient will not be directly exposed to the suspicious drug. However, specific-IgE and/or basophil activation testing used to diagnose immediate reactions are limited to a few compounds. Moreover, despite its good specificity, there is a lack of sensitivity for most of these tests. This means that it is not possible to exclude a suspicious drug only with a negative test.¹ Besides that, the lymphocyte transformation test for non-immediate reactions is not standardized, limiting its use outside the research setting.⁶

Skin tests are the most readily available tool for the evaluation of suspected immediate-onset IgE-mediated drug hypersensitivity. They are safe and provide evidence of sensitization to a specific drug, but must always be interpreted within the appropriate clinical context. Skin tests are simple to perform. There is no need for performing all skin testing in a hospital setting, except possibly for a few high-risk patients. They are low-cost procedures, as just the drug, a control, and histamine are required. The results are quickly obtained; generally less than 1 hour is needed to perform both immediate reading prick and

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Abbreviations used

AAAAI- American Academy of Allergy, Asthma, and Immunology
BL- Beta-lactam
DHR- Drug hypersensitivity reaction
DPT- Drug provocation test
EAACI- European Academy of Allergy and Clinical Immunology
EHR- Electronic health record
ENDA- European Network for Drug Allergy
MDM- Minor determinate mixture
NSAID- Nonsteroidal anti-inflammatory drug
PPL- Benzylpenicilloyl-poly-L-lysine
SCAR- Severe cutaneous adverse reaction
TRPA1- Transient receptor potential ankyrin 1

intradermal testing. Moreover, they can be highly specific, with few false-positive results.¹

However, they cannot be considered the ideal test because of the variation of sensitivity and predictive values, which depend on the culprit drug and the clinical presentation of the reaction. Thus, a negative skin test can be unreliable for ruling out drug hypersensitivity. To minimize false-negative or false-positive results, various factors should be considered:

- (i) Is the native drug in its reactive form, or is a drug metabolite responsible for the reaction and not the parent drug?
- (ii) Many drugs are haptens and have to be conjugated with a carrier protein before being a complete allergen.
- (iii) Drug use may interfere with test results, especially antihistamines and corticosteroids.
- (iv) Is the correct concentration and vehicle for each type of skin test and drug well documented in the literature?

The European Network for Drug Allergy (ENDA) and the European Academy of Allergy and Clinical Immunology (EAACI) have elaborated a position paper on skin test concentrations for systemically administered drugs.⁷ When the test has not been validated, start with a low concentration, usually 1/100 of the concentration used for intravenous administration. If no reaction occurs, increase the concentration 10-fold, until a positive reaction occurs. Finally, test the drug in the concentrations used in 10 healthy subjects, without a history of potential hypersensitivity, to avoid false-positive results from direct irritating reactions.⁷

Skin tests are currently recommended by the AAAAI and the EAACI as a first-line investigation procedure for the diagnosis of suspected immediate-onset allergic reactions to drugs, as they are less risky than the DPT. The EAACI also recommends patch tests and delayed reading intradermal tests for nonimmediate reactions.⁸

The DPT is indicated in both American and European perspectives mainly to exclude hypersensitivity in a nonsuggestive history of DHR and to provide safe alternatives in allergic patients. However, the EAACI/ENDA also recommend performing the DPT to exclude cross-reactivity of related drugs in proven hypersensitivity and to establish a firm diagnosis of DHR when allergy tests are negative, inconclusive, or nonavailable.⁴ In the last 2, there can be an increased risk of reaction, and therefore, a strong indication for skin testing, considering that a positive result would avoid unnecessary exposure to the drug.

Jares et al⁹ highlight the importance of performing skin tests before the DPT in a multinational experience with DHR in 862

patients in Latin America. In this study, skin prick tests were performed in 145 (17%) patients with positive results in 56 (30%) and intradermal tests in 91 patients with a positivity rate of 40%. All of these patients had a relevant clinical history and were thus considered allergic, avoiding the risk of reacting during a DPT. Unfortunately, the study also shows that less than 30% of patients with a suspicious DHR are thoroughly investigated in that region.⁹

Avoiding the risk of a new reaction is particularly important for patients who have presented with an anaphylactic reaction. Anaphylaxis is the most common life-threatening condition related to DHR, and drugs are not just reported as the most common trigger, but also responsible for almost 60% of anaphylaxis fatalities.^{10,11} The diagnosis in those cases is of utmost importance because 67% of patients reported a previous reaction with the same drug used in the current reaction.¹² Among patients with drug-induced anaphylaxis in another multicenter study in Latin America, prick tests were positive in 41% of 78 tests performed in 60 patients with drug-induced anaphylaxis, and in 48% of 54 intradermal tests in 30 patients.¹³ These patients were at a high risk for a DPT, and a positive skin test would be enough for a diagnosis.

Despite not being the primary cause of drug-induced anaphylaxis in Latin America, where NSAIDs account for more than 50% of reactions (including children), antibiotics are reported as the most frequent drug related to acute-onset severe hypersensitivity reactions in North America and Europe.¹²⁻¹⁶ Among the antibiotics associated with DHR, beta-lactams (BLs) are most commonly implicated.¹⁷

Several groups have proposed rational approaches to the patient with a history of an immediate-onset potentially IgE-mediated reaction to a BL.^{18,19} Some of them recommend using specific serum-IgE to penicillin, amoxicillin, and ampicillin for initial screening, despite its low sensitivity, but most agree that skin tests should be performed before DPT. However, the commercial availability of standardized penicillin skin test reagents, including the major determinant benzylpenicilloyl-poly-L-lysine (PPL) and the minor determinates benzylpenicillin, amoxicillin, clavulanic acid, benzylpenilloate, and benzylpenicilloate, around the world varies, and this limits their use. A combination of typically benzylpenicillin, benzylpenilloate, and benzylpenicilloate is called the minor determinate mix (MDM).

In both American and European practice guidelines, skin testing using PPL (5×10^{-5} mol/L), MDM (2×10^{-2} mol/L), and BP (10,000 IU/mL) is currently recommended, despite MDM not being commercially available in the United States. In Europe, skin testing using amoxicillin (20 mg/mL) and ampicillin (20 mg/mL) is recommended, as amoxicillin is currently the most commonly used penicillin and the primary elicitor of hypersensitivity reactions.⁸

The lack of standardized reagents in some countries, combined with other factors that lead to an incorrect diagnosis, such as mislabeling of a side effect (eg, gastrointestinal upset), "allergic" symptoms caused by a concomitant underlying infection, loss of sensitivity over time due to avoidance of the drug, or absence of cofactors, all may contribute to the low rate of skin test positivity in some recent studies. On the other hand, it is a procedure that can identify 9 in 10 patients who could receive penicillin safely, even when considering a suggestive history of penicillin allergy.²⁰

Ramsey and Staicu²¹ recently reported the utility of using a penicillin allergy history algorithm associated with skin tests in

selected patients under treatment with second-line antibiotics to have a safe transition to first-line BL antibiotics. This complies with a worldwide effort to remove the inaccurate label of “penicillin allergy” from many patients as possible who are overdiagnosed, thus reducing the costs of medical care.^{22,23}

In our experience at the Federal University of São Paulo, this has been our primary challenge, because most of our patients have an unreliable history of penicillin allergy. Moreover, we have not seen many positive tests to BLs, except for some related to perioperative anaphylaxis, especially with cephalosporins. By all means, positive skin tests to these drugs could be “false positive,” as reported by Tannert et al,²⁴ but we believe with a good history, and using standardized drug concentrations, we could minimize inaccurate results. We have also observed that many patients are afraid of performing a DPT, even with a nonsuggestive history of drug allergy. For these patients, skin tests before DPT could be beneficial, as they feel more confident that the reported reaction might not have been a real allergic reaction.

We propose a strategy for BL immediate hypersensitivity diagnosis and risk stratification that could also be used to assess cross-reactivity. A similar approach has been suggested by others, with whom we are in accordance (Figure 1).^{18,25} Low-risk patients are those with a nonsuggestive history or only mild reactions, such as isolated urticaria or other benign rash. These patients do not need a skin test before DPT, as the chance of a critical reaction is reduced. Patients with a history of 2 or more repetitive reactions to BL antibiotics, independent of the severity of the reactions, or with angioedema or anaphylaxis, are at high risk of developing a reaction during the DPT, and should be skin tested first. We also recommend skin tests before DPT for those patients who do not feel safe in performing the DPT, irrespective of the severity of the historical reaction. For patients at the highest risk, specifically pregnant women with syphilis and a reliable history of penicillin allergy and negative or nonavailable skin tests, we consider desensitization without a DPT.

Summary of the pro position

Skin tests are useful in confirming and excluding a diagnosis of drug hypersensitivity. Drug concentrations must be validated and results must be carefully assessed. Positive skin tests help avoid unnecessary risks associated with re-exposure in high-risk patients.

THE CON POSITION—DR MACY

I will concentrate my comments on the specific case of suspected penicillin hypersensitivity, because penicillin “allergy” is the most commonly reported drug “allergy” and there is an extensive literature on penicillin hypersensitivity testing. These general concepts, however, are also applicable in the evaluation of suspected hypersensitivity to other drugs.

There are 4 immunologically mediated drug hypersensitivity clinical presentations, acute-onset benign (typically urticarial rashes), acute-onset life-threatening (anaphylaxis), delayed-onset benign (typically maculopapular rashes), and delayed-onset life-threatening (SCARs).²⁶ The immunologic mechanisms responsible for these drug hypersensitivity presentations include IgE, IgG and complement, nanoparticle complement activation, and direct mast cell activation for acute-onset benign reactions; IgE, IgG and complement, nanoparticle complement activation, and direct mast cell activation for acute-onset life-threatening

reactions; T cells for delayed-onset benign reactions; and T cells or IgG-dependent T-cell-mediated for delayed-onset life-threatening reactions.²⁷ Acute- and delayed-onset life-threatening reactions are the reactions of most concern and, as will be shown later, are extremely rare.

Acute-onset benign cutaneous reactions account for only approximately 2% to 3% of all individuals with a penicillin “allergy” history. Acute-onset severe systemic reactions, anaphylaxis, accounts for less than 0.1%. Delayed-onset benign cutaneous reactions account for 1% to 2%. SCARs account for much less than 0.1%. Something completely else, but clearly not an immunologically mediated reaction, such as a pharmacologic reaction, expected side effect, headache, yeast infection, gastrointestinal upset, viral exanthem, other benign reaction or association, fear, or some unknown reaction, account for the majority of penicillin “allergies” reported in the electronic health record (EHR), approximately 95% to 97%.²⁸

In EHR data from 2,375,424 Kaiser Permanente Southern California members who had a health care visit and at least 11 months of health care coverage during 2009, at least 1 drug intolerance was reported in 25.1% of females and 14.2% of males.²⁹ At least 1 antibiotic intolerance was reported by 16.7% of females and 8.8% of males. The most commonly reported specific drug intolerance was to penicillins, noted by 9.46% of females and 5.93% of males. In a cohort of 1,766,328 patients who attended 2 large tertiary care hospitals in Boston from 1990 to 2013, 35.5% of patients had at least 1 reported drug intolerance with an average of 1.95 drug “allergies” per patient for those reporting any intolerance.³⁰ Again, the most commonly reported drug intolerances, in this somewhat older population, were to penicillins, with 12.8% reporting an “allergy.” An unconfirmed penicillin “allergy” is a significant health risk and testing can significantly lower this risk.^{22,31,32} There are millions of patients who need to have their penicillin hypersensitivity confirmed or removed.

The history of the penicillin-associated reaction is the key to determining a potential mechanism of the reaction and the risks of testing and challenges.²⁶ Reactions that start within hours of the first dose of the last course are much more likely to be IgE mediated. Reactions that start 2 to 5 days after course initiation are much more likely to be T-cell mediated. Hives are more likely to be associated with IgE-mediated reactions and maculopapular rashes are more likely to be associated with T-cell-mediated hypersensitivity. History, however, is inadequate to confidently establish current clinically significant hypersensitivity or current tolerance.

The current best estimate for penicillin-associated anaphylaxis rate is much lower than previously thought, and commonly feared, only approximately 1 in 225,000 with oral exposures and approximately 1 in 80,000 with parenteral exposures.³³ Thus, if approximately 1% of all penicillin exposures result in a new “allergy” report, less than 1 in 1000 penicillin “allergies” are from anaphylaxis. The risk of causing death with an oral amoxicillin exposure is also known to be extremely low, with only 1 fatality associated with oral amoxicillin use noted in more than 100,000,000 amoxicillin courses given in Great Britain over a 35-year period.³⁴

Penicillin-associated SCARs are even rarer than anaphylaxis. There are no good population-based data on the incidence of confirmed penicillin-associated SCARs. For all cases of Stevens-Johnson syndrome and toxic epidermal necrolysis,

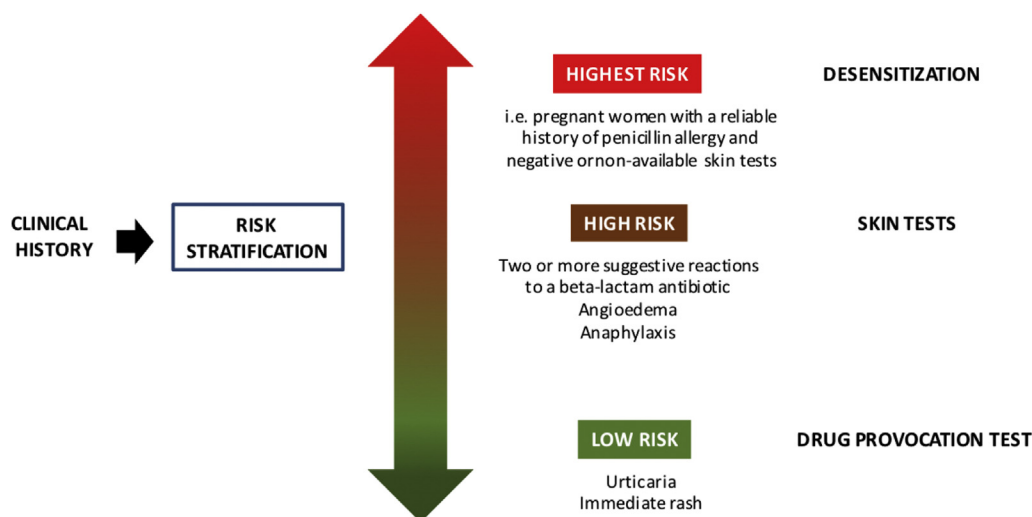


FIGURE 1. Diagnosis and risk stratification strategy used at the Federal University of São Paulo for beta-lactam immediate hypersensitivity reactions.

85% are drug associated and there are only approximately 1 to 2 cases per million population per year. The drugs most commonly associated with SCARs are antiseizure medications (specifically aromatic anticonvulsants including phenytoin, phenobarbital, carbamazepine, and lamotrigine, but rarely valproic acid), antiretroviral agents, allopurinol, NSAIDs, and antibiotics.¹⁹ Because viral infections can also be associated with SCARs, some of the attributions to antibiotics may be coincidental.

The current reference standard test to confirm acute- or delayed-onset clinical tolerance to penicillins is an oral challenge with a therapeutic dose of amoxicillin.²⁶ Amoxicillin is used because it accounts for up to 80% of all penicillin-class antibiotic used and has the essential core structures responsible for most penicillin-associated immunologically mediated hypersensitivity. There are also rare individuals with immunologically mediated hypersensitivity directed only to the amoxicillin side chain. Typically, 1 hour of observation after a single oral amoxicillin 250 mg dose is used to confirm the lack of clinically significant IgE-mediated acute-onset hypersensitivity. Up to 3 to 5 hours of observation is used to confirm the lack of clinically significant IgG and complement- or direct mast cell activation-mediated acute-onset hypersensitivity. Up to 5 days of observation is used to confirm the lack of clinically significant T-cell-mediated delayed-onset hypersensitivity. A negative oral challenge also helps convince the patient, and other treating physicians, that it is OK to use penicillins in the future. After a negative oral challenge, it is very important to clearly document the specific tests and/or challenge performed and link the negative results to the previously reported penicillin “allergy.” This will help ensure that the penicillin “allergy” is not restated without a new penicillin-associated adverse reaction.

Skin testing is done to reduce the risk of anaphylaxis with challenges. Skin testing, however, carries the risk of false-positive results that can result in continued avoidance, use of antibiotics with higher risk profiles, and/or the time and expense of desensitization.

Just selecting an alternative drug in the setting of a reported drug intolerance is not always benign. All drugs have side effects. There is a predictable rate of new drug intolerances that will be reported after every therapeutic drug use. Some drugs benefit certain individuals more than other drugs. These effects vary with age and underlying genetics. Alternative medication use may have a higher likelihood of inducing an adverse reaction or resulting in a therapeutic failure. The primary risk of testing is having a reaction associated with the testing or a reaction with future therapeutic use, because the testing is inaccurate. An oral challenge with a therapeutic dose virtually excluded this risk. Most drug-associated immunologically mediated hypersensitivity rechallenge reactions would be expected to have a similar severity to the index reaction.

Just because skin testing before rechallenge can be useful or comforting, it does not mean that it is always mandatory or even necessary. Penicillin skin testing, particularly if done with high-dose reagents and using very low criteria for a positive result, can even cause additional problems by resulting in failure to proceed to an oral challenge, continued penicillin avoidance, and the morbidity associated with the needless avoidance. Needless complex protocols using difficult to procure reagents limit utility and lead to no testing being performed.

Skin testing is primarily performed to reduce the risk of a recurrent acute-onset severe systemic reaction, anaphylaxis, associated with rechallenge. Skin testing is only useful for drugs that can effectively haptenate serum proteins or are intact antigens. Skin testing is associated with frequent false positives and false negatives. Well-validated protocols are available for protein antigens and only very few drugs that haptenate, including penicillins.

Many penicillin skin test results are false positives, particularly if a low threshold, such as a 3-mm wheal, is used to define a positive test result, or if high concentrations, >0.01 molar, of reagents are used.²⁵ Females will more commonly have these false-positive skin test results if 3 mm of wheal is used as the criteria for a positive result.^{35,36} This sex difference disappears in

TABLE 1. Kaiser Permanente San Diego penicillin allergy test results (January 1, 2017 to December 31, 2017)

• 620 children and adults
• 222 (35.8%) had penicillin skin testing first
• 3 (1.4%) skin test positive
• 3 (1.4%) acute-oral challenge positive after negative skin testing
• 398 (64.2%) had direct oral amoxicillin 250 mg challenge
• 1 (0.3%) acute-onset oral challenge positive
• 5 (1.3%) delayed-onset oral challenge positive
• Overall 12 (1.9%) positive
• 7 (1.1%) acutely positive (IgE-mediated)
• 5 (0.8%) delayed-onset positive (T-cell-mediated)
• 21 (3.4%) subjective oral challenge reactions

None of the reactions were serious and all were managed with oral antihistamines or intramuscular adrenaline.

the Park study when the data are recalculated using 5 mm of wheal as the criteria for a positive result.³⁷

Mill et al³⁸ gave direct oral amoxicillin challenges to 818 children with a history of penicillin “allergy” and noted only 17 acutely positive challenge reactions. When these individuals underwent penicillin skin testing, only 1 was positive. Had all 818 children been skin tested initially, there would have been significantly more than 1 positive result, and most of the positive results would have had negative oral challenges. Tucker et al³⁹ gave direct oral amoxicillin challenges to 328 Marine recruits with a history of penicillin “allergy,” and only 5 (1.5%) had any acute objective reaction.

There are also several potential mechanisms for non-IgE- and non-histamine-mediated acute-onset hypersensitivity symptoms induced by penicillins. Penicillins can activate the RhoA/Rock signaling pathway that affects endothelial hyperpermeability.⁴⁰ Tannert et al⁴¹ recently reported that histamine was only detected in the minority of positive intracutaneous penicillin skin tests by microdialysis. Penicillin can also potentially selectively activate a sensory ion channel, the transient receptor potential ankyrin 1 (TRPA1), in dorsal root ganglion neurons in a murine system. Pharmacologic inhibition or genetic ablation of TRPA1 abolishes or greatly attenuates this penicillin-induced nonallergic skin reaction. Piperacillin, with a bulkier side chain than penicillin or amoxicillin, had no effect on TRPA1 (unpublished data from Jian Yang, Department of Biological Sciences, Columbia University, New York).

Our current penicillin hypersensitivity evaluation protocol at Kaiser Permanente Southern California is as follows. We consider penicillin skin testing first if:

- (1) the penicillin-associated reaction occurred within the past 12 months, and was clinically compatible with an IgE-mediated allergy;
- (2) the patient has any history of shortness of breath or anaphylaxis associated with penicillin; and
- (3) if the patient, or the physician, is afraid of a direct oral challenge.

We only skin test, both puncture and intradermal, with penicilloyl-polylysine (PrePen) and per package insert use of a 5-mm wheal with flare greater than wheal as the criteria for a positive result. We then proceed to an oral amoxicillin 250 mg

challenge in all skin test negative individuals to confirm current tolerance.

A direct oral amoxicillin challenge can be performed in any patients with a history of one of the following penicillin-associated symptoms:

- (1) a benign rash occurring more than 12 months ago
- (2) gastrointestinal symptoms
- (3) headaches
- (4) other benign somatic symptoms
- (5) unknown symptoms.

Recent Kaiser Permanente San Diego penicillin hypersensitivity testing results are displayed in [Table 1](#).

Just because nonirritating concentrations of drugs have been published, it does not mean these drugs effectively haptenate serum proteins, are intact antigens, or predict clinically significant IgE-mediated allergy. Many drugs are direct, IgE-independent, mast cell activators.^{42,43} The risk of a recurrent reaction is based on the severity of the index reaction. Would the patient be willing to have a repeat reaction? There are many drugs where direct rechallenge is the management plan of choice and/or skin testing is of no diagnostic value. Common examples include NSAIDs, macrolide antibiotics, sulfonamide antibiotics, and opiates.

Summary of the con position

The reference standard to confirm clinically significant penicillin hypersensitivity is an oral amoxicillin challenge. A direct oral challenge can be safely used in most penicillin “allergic” individuals with low-risk histories. Penicillin skin testing with penicilloyl-polylysine is useful in reducing the risk of anaphylaxis with an oral amoxicillin challenge in individuals with high-risk histories, without causing excessive false-positive results.

CONCLUSIONS

When evaluating a patient with drug hypersensitivity, it is important to balance the risks and benefits of continued avoidance versus any testing and/or rechallenge protocol considered. Skin testing can, in limited settings with higher risk patients, provide an additional level of safety, before a confirmatory oral challenge. Skin testing cannot establish, by itself, current tolerance.

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