# ABOUT THE AUTHOR

## Moshe Ben-Shoshan, MD

Dr. Ben-Shoshan graduated from The Sackler School of Medicine, Tel-Aviv, Israel and completed his fellowship in pediatric allergy/clinical immunology at Montreal Children's Hospital in 2009. Dr Ben-Shoshan is currently a physician in the division of Allergy/ Immunology at Montreal Children's Hospital and is involved in research initiatives on anaphylaxis, chronic urticaria and immunodeficiency. He recently established the first worldwide cohort to assess children with suspected antibiotic allergy through graded challenges for which he received a CIHR grant, and together with Dr. Bruce Mazer established the first rigorously designed and evaluated program in Canada for milk desensitization and more recently they have established protocols for peanut, tree nut and egg desensitization. His research has resulted in more than 100 published manuscripts and his work on the diagnostic approach of antibiotic allergy in children has led to a fundamental shift in clinical practice for the diagnosis and management of amoxicillin allergies in children. This study was named a top 10 publications worldwide for pediatrics in 2016 by the *New England Journal of Medicine* Journal Watch.

# AMOXICILLIN ALLERGY: OLD CONCEPTS, NEW CONCEPTS AND CHANGE OF CONCEPTS

## BACKGROUND

More than one million Canadian children are treated annually with antibiotics, mainly amoxicillin.[1-4] Up to 10% of children develop rashes while treated with amoxicillin.[1-5] The majority of children presenting with rashes during amoxicillin treatment are diagnosed with amoxicillin hypersensitivity without further evaluation and often carry this diagnosis into adulthood .[1]

There remains controversy in the medical literature regarding the most accurate and safe strategy for diagnosing amoxicillin hypersensitivity.[1,5,10-13] As a result, most children continue to avoid amoxicillin and other penicillin derivatives throughout life in favor of alternatives that are reported to be less effective, more toxic, and more expensive.[12-16]

There is much we do not know about the pathogenesis of amoxicillin hypersensitivity. Consequently, the appropriate diagnostic strategy required to establish the presence of true amoxicillin hypersensitivity is unclear. In order to develop an appropriate diagnostic approach, it is important to understand the pathogenic mechanisms accounting for amoxicillin hypersensitivity and the validity of the available confirmatory tests. This review will discuss the pathogenic mechanisms underlying amoxicillin allergy, describe the challenges in the diagnosis of amoxicillin allergy, critically assess the role of skin testing and IgE levels and discuss the appropriate diagnostic strategy in individuals presenting with suspected amoxicillin allergy.

## A.THE PATHOGENESIS OF AMOXICILLIN ALLERGY

Until recently, it was believed that all immediate reactions to amoxicillin were IgE mediated. However, recent studies suggest that other mechanisms related to allotype interactions between the drug and specific HLA molecules play a major role in both immediate (occurring within one hour of exposure) and non-immediate reactions (occurring more than one hour after exposure)[10] to amoxicillin.

The term "drug allergy" refers to a specific immune response to a drug acting as hapten, and is directed against a hapten-carrier complex, which functions as an

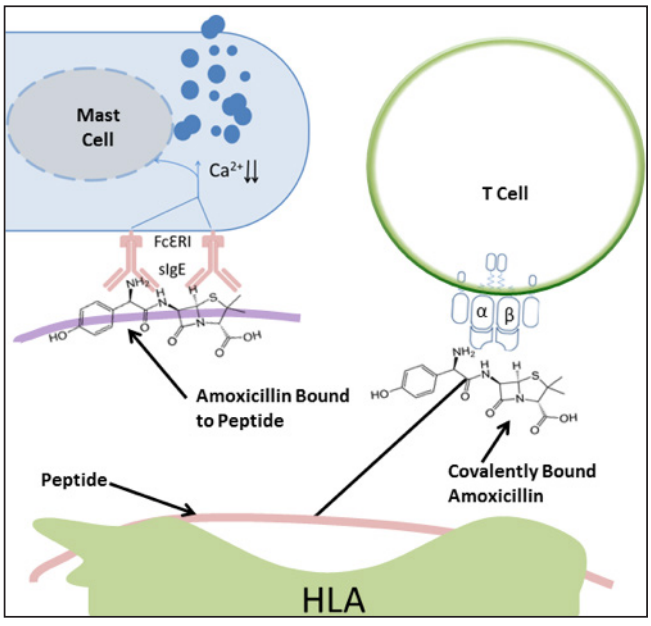


*Figure 1. Drug hypersensitivity as a result of covalent binding of drugs to proteins ; courtesy of Moshe Ben-Shoshan, MD*

allergen. In contrast, the term drug hypersensitivity (DH) goes beyond drug allergy. It includes, in addition to the aforementioned allergy definition, reactions of immune or inflammatory cells, which are not due to a hapten-protein antigen. Studies suggest three main forms of DH:[17]

The first form of hypersensitivity relies on the covalent binding of drugs to proteins, which then form new antigens, to which a humoral and/or cellular immune response can develop that will cause DH in subsequent exposure (**Figure 1**). This pathogenic mechanism has led to a reliance on skin tests with major and minor penicillin allergens for the diagnosis of amoxicillin allergy. However, given that at least 50% of DH to amoxicillin is reported to occur with the first exposure[5] and given that tests relying on the detection of specific humoral and/or cellular immune responses to amoxicillin are negative in most cases of amoxicillin associated DH, this mechanism is unlikely to play a major role in the majority of cases with amoxicillin DH.[5]

The second form of DH ("pseudo-allergy") is represented by drug interactions with receptors of inflammatory cells, which may lead to their direct activation or enhanced levels of inflammatory products (**Figure 2**).[20] Specific IgE or T cells are not involved.[10] Given that these reactions usually involve drugs containing tertiary and quaternary ammonium structures (present in quinolones e.g. but not in amoxicillin) binding to the G-protein-coupled receptor X2 (MRGPRX2),[20] amoxicillin hypersensitivity reactions are unlikely mediated by this pathway.

Finally, the p-i (pharmacological interaction with immune receptor) concept represents an off-target activity of drugs with immune receptors (HLA or TCR), which can result in unorthodox, alloimmune-like stimulations of T cells that will lead to immediate/ non-immediate DH reactions even upon first exposure. Some of these p-i stimulations occur only in carriers of certain HLA alleles and can result in clinically severe reactions (**Figure 3**).

Recent studies suggest that amoxicillin related hypersensitivity reactions are mainly related to the third form of DH reactions.[17] In these cases drug-dependent but not necessarily antigen-dependent stimulation of immune competent cells like T cells and/or inflammatory cells by drugs occurs.[18] This premise, although not well established yet for amoxicillin, is supported by several studies for beta lactam antibiotics in adults as well as for other drugs.[17] Drug-naïve patients (almost 50% of children reacting in some cohorts[5]) often react with hypersensitivity reactions to amoxicillin, an unlikely phenomena according to the Gell and Coombs classification (form 1).[5] In addition, limited data reported for drugs including beta lactams in adults, suggest that it is possible to predict drug hypersensitivity through the identification of a patient's specific genetic HLA markers.[17,19,20]

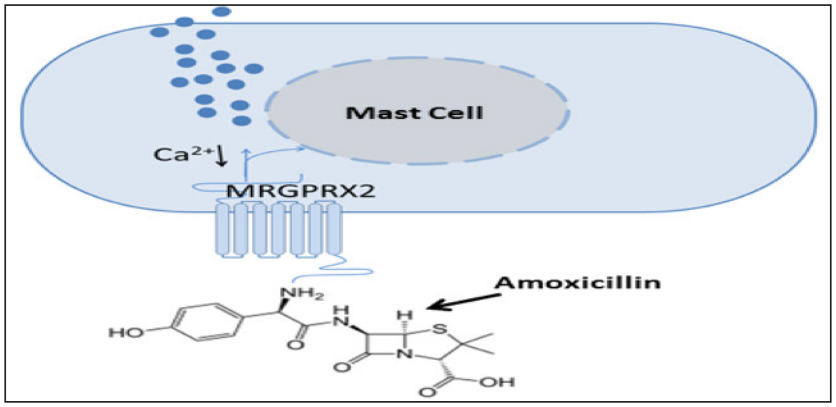


*Figure 2. Drug hypersensitivity as a result of drug interactions with receptors of inflammatory cells; courtesy of Moshe Ben-Shoshan, MD*

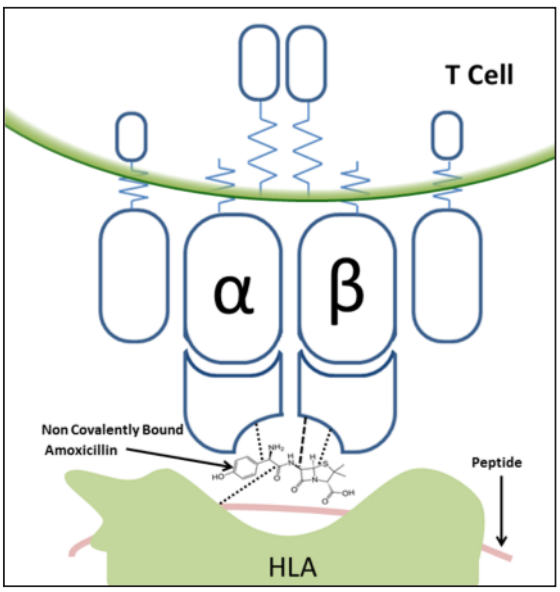


*Figure 3. Drug hypersensitivity as a result of pharmacological interaction with immune receptors; courtesy of Moshe Ben-Shoshan, MD*

## B. CLINICAL FEATURES OF AMOXICILLIN ALLERGY

Studies reveal that immediate reactions to amoxicillin – defined most often as reactions occurring within the first hour after exposure-- as well as non-immediate reactions usually present with cutaneous symptoms only. These symptoms may include hives, macular / papular rashes as well as serum sickness-like reactions (SSLRs) (**Figures 1A, B and C**).[5,22] It is noteworthy that studies suggest that patients' self-reported history has low accuracy and concordance with an actual diagnosis of penicillin allergy.[23]

Benign reactions are limited to the skin, present often as maculopapular exanthemas/ urticaria and do not involve mucosal surfaces, or blisters. SSLR is characterized by large erythematous urticarial plaques with dusky to ecchymotic centers, often associated with hand and foot swelling that develop 7 to 21 days after medication exposure.[24] In addition to the characteristic cutaneous manifestations, patients with SSLRs are reported to have fever, malaise, lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, myalgias, headaches and self-limiting symmetric arthritis.[24] Similarly, in rare cases, viral infections can be associated with a similar rash called urticaria multiforme.[25] Although SSLRs have the important property of benignity, until recently it has been recommended to avoid amoxicillin in any suspected

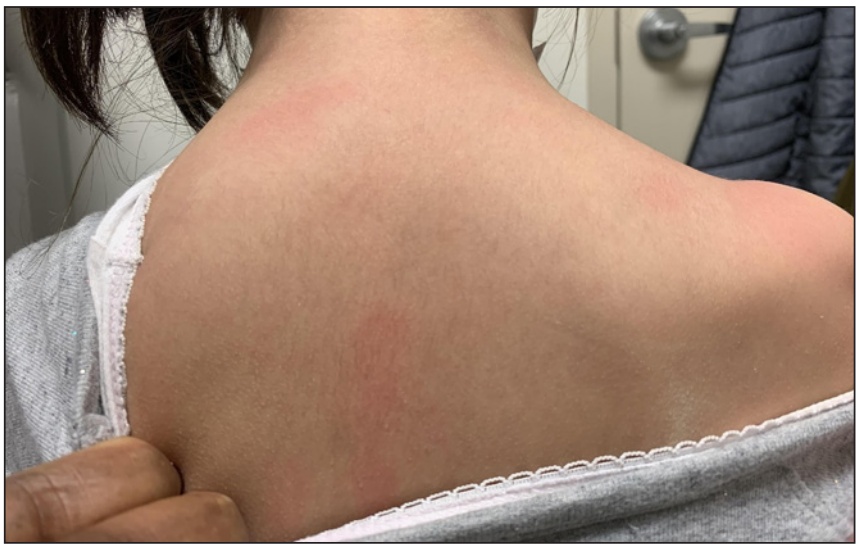

*Figure 1A. Immediate reaction to amoxicillin in a 6-year-old girl within 15 minutes of amoxicillin challenge; photo courtesy of Moshe Ben-Shoshan, MD*

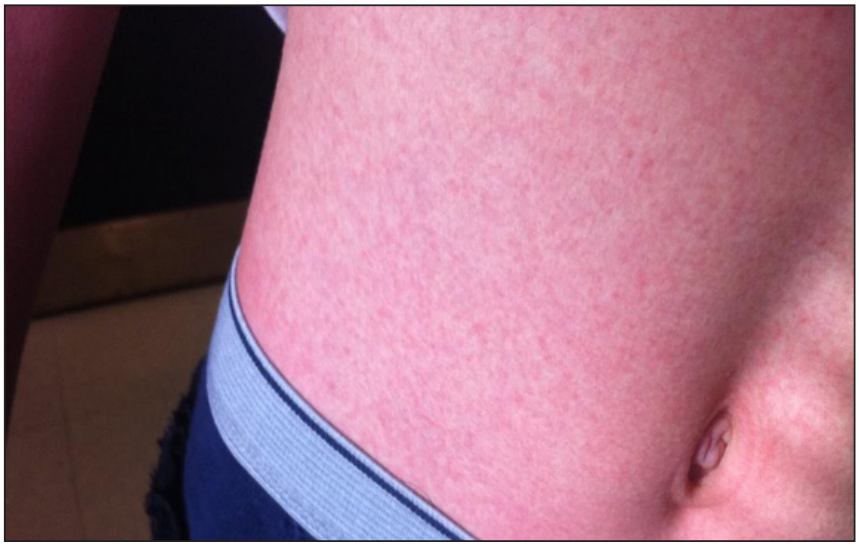

*Figure 1B. Non-immediate reaction to amoxicillin in a 17-year-old boy 8 hours after amoxicillin challenge; photo courtesy of Moshe Ben-Shoshan, MD*

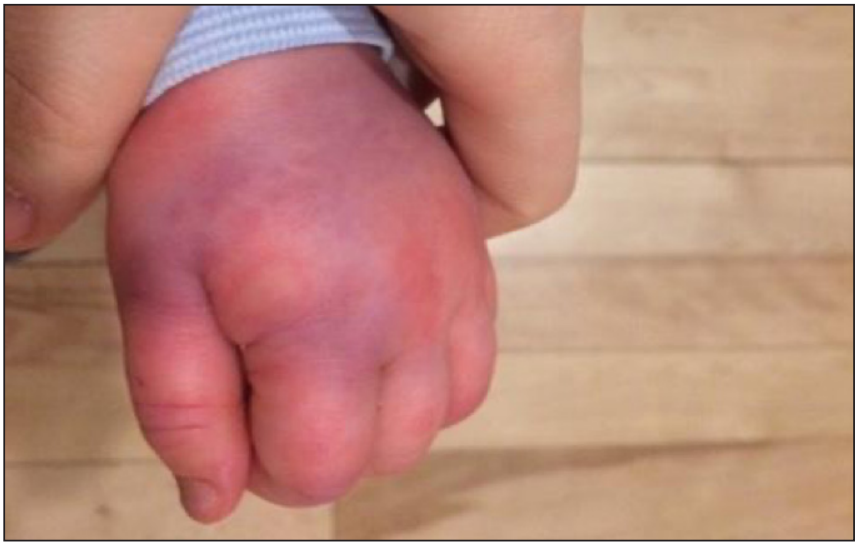

*Figure 1C. SSLR in an 8-month-old baby after 7 days of amoxicillin treatment (photo exemplifies hemorrhagic lesions and swelling of wrist ); photo courtesy of Moshe Ben-Shoshan, MD*

case of SSLR without further investigation. More recently, however, the literature has shown that a dose provocation test (DPT) can be safely used in children (n=75, median age= 2.0 years) presenting with suspected SSLR. Investigators were able to demonstrate that positive immediate reaction to the DPT occurred in 2.67% of subjects, a positive non-immediate reaction to the DPT occurred in 4%, and of the 43 patients successfully contacted, 20 reported subsequent culprit antibiotic with 25% of these subjects experiencing reactions that were mild and limited to the skin.[22]

More rarely, reactions to amoxicillin may present as anaphylaxis when at least two organ systems or hypotension are involved in the hypersensitivity reaction.[26] Although these cases represent an important entity, they are rarely appropriately diagnosed. In a study conducted by our group, we reported that the majority of adult and pediatric cases presenting to the emergency room with suspected antibiotic-associated anaphylaxis, were not appropriately diagnosed. Of the 18 (40%) children that presented to the emergency room, only 10 (55.5%) patients had seen an allergist for assessment. Of these ten children, seven underwent skin testing, of which one was positive to ceftriaxone by intradermal skin testing. Among the six with a negative skin test, two proceeded to a graded oral challenge, which was positive in one case to amoxicillin (mild cutaneous reaction). For adults with suspected antibiotic associated anaphylaxis, only 33.3% had been assessed by an allergist. Of these patients only one patient underwent skin testing which was negative, and that same patient underwent a graded oral challenge which was positive to cefadroxil (mild cutaneous reaction).[27] Other rare presentations include Stevens-Johnson syndrome, and toxic epidermal necrolysis.[28] In these cases, the future use of amoxicillin should be **avoided**, and a diagnosis should be made based on the clinical presentation. Some studies suggest that the use of a skin biopsy can confirm the clinical diagnosis and delayed hypersensitivity tests, especially the patch test and the lymphoblastic transformation test (LTT)[29] may be important in validating the etiological diagnosis, although their validity is not well established.

Fatality related to amoxicillin allergy is extremely rare. The risk of fatal anaphylaxis with penicillin has previously been estimated to be about 1 in 100,000 and is greater in those receiving penicillin parenterally than orally.

Various risk factors have been hypothesized to increase the risk of amoxicillin hypersensitivity. Limited data in adults suggest that beta lactam allergy is more common in females.[31,32] Certain co-morbid conditions including immunosuppression and cystic fibrosis are reported to increase the risk of true amoxicillin hypersensitivity.[12] Other factors include previous exposure to the implicated medication, prolonged dose and duration of the implicated medication, route of administration (with parenteral and cutaneous routes more sensitizing),[33] and concurrent viral infection (up to 100% of children and adolescents with Epstein-Barr virus with rash if on amoxicillin).[34] However, the effect of these factors has not yet been established in children to date.

## C. LIMITATIONS OF CURRENTLY USED STRATEGIES TO DIAGNOSE AMOXICILLIN HYPERSENSITIVITY

The diagnosis of amoxicillin hypersensitivity is challenging. The traditional approach relies on intradermal skin tests and, if negative, a drug challenge is recommended. The validity of a test is defined as its ability to distinguish between those who have a disease and those who do not.[35] Thus, the validity of such an approach is best judged based on studies assessing the sensitivity and specificity of the skin test compared to the gold standard test (i.e. drug challenge ). A critical appraisal of the few studies challenging all cases with suspected drug allergy reveals that the validity of available skin tests is, at best, questionable.[5,36] Recent studies[5,36,37] underscore that available standardized skin tests (skin prick and intra-dermal tests with Pre-Pen, or penicillin G) for children have a limited role

in the diagnosis of immediate reactions to penicillin derivatives with a sensitivity of less than 10% and positive predictive value of 30%.[5,36,37] Moreover, it was concluded that skin tests may result in a false positive rate in up to 80% of pediatric cases who tolerate the culprit beta lactam antibiotic when challenged.[36] In addition, skin tests have no role in the diagnosis of non-immediate reactions[38,39] and for non-penicillin beta-lactam antibiotics where there are no standardized skin tests.[40]

Recently a new kit for penicillin evaluation containing the major allergenic determinant (penicilloyl polylysine), a minor determinant mixture (penicillin G, penicilloate, penilloate), and amoxicillin was reported to have a negative predictive value of 98%.[41] The interesting aspect about positive and negative predictive values is that they change when the prevalence of the disease changes. In fact, for any diagnostic test, the positive predictive value will fall as the prevalence of the disease falls while the negative predictive value will rise.[42]

A low prevalence simply means that the person we are testing is unlikely to have the disease and therefore, based on this fact alone, a negative test result is likely to be correct.[42] Two recent systematic reviews report a positive predictive value of skin tests in children of 33%,[43,44] leading to a high rate of inaccurate diagnosis and the risk of mislabelling.

## D.USE OF DIRECT DRUG PROVOCATION TEST

Although a DPT is considered the gold standard for diagnosis,[39] it has been rarely used in practice, owing to a lack of data regarding its safety and accuracy in children. Prior to 2016 it was considered unethical to challenge children with a suspected antibiotic allergy in the absence of skin tests. However, recent studies[5,22,36,40] reveal that in children this approach is safe and ethically acceptable in cases of non-severe reactions limited to the skin[45] including SSLRs.[22] Moreover, given that skin tests are negative in more than 95% of cases, an oral challenge is ultimately needed to confirm tolerance in most of these children.[5,22,36,40] Positive challenges are rare, and even where children have reproducible signs on challenge, they rarely constitute immediate or serious symptoms.[5,22,36,40]

A DPT may be conducted in one or two-step doses (10% of the therapeutic dose, then 20 minutes later 90% of the therapeutic dose). We have shown that among children with immediate reactions undergoing a two-step challenge, almost one third reacted within 20 minutes after the first dose and that among those who had a non-immediate reaction (defined as more than one hour after the challenge), almost a third reacted more than 24 hours after the challenge (up to five days ). All reactions were classified as mild.[5] Hence, it is recommended to follow patients one week after a negative DPT to document potential late reactions. Challenges should be conducted only in the allergy clinic in the presence of an allergist and/or health care providers that are trained and have the required equipment to treat adverse reactions. Following a DPT, observation time should be at least one hour with DPT over a longer time interval, such as five to seven days having also been suggested.[46] However, a lengthier challenge also exposes patients to the risk of bacterial antibiotic resistance development, making subsequent use of antibiotics ineffective.[47] Furthermore, recent studies suggest a lack of value for prolonged challenge in cases with suspected antibiotic allergy[48] and indicate that the vast majority of cases of nonimmediate reactions may be captured by a one-day challenge.[49] It is also possible that in some cases the diagnosis of an antibiotic allergy in the context of infection could be related to the interaction between a viral infection and the antibiotic.[50-52] It should be noted that the negative predictive value of a DPT is reported to be 89% (49 out of 55) and 10% of cases (6 out of 55) with a negative DPT were reported to have developed mild skin reactions on subsequent future use.[5]

Most data regarding the use of DPT to diagnose amoxicillin/penicillin allergy are based on pediatric studies,[5,22,36] More

recently, a limited number of studies suggest that this approach may be used in adults presenting with benign skin rashes. In one study of 156 adults, 2.6% of subjects reacted to a DPT. Interestingly, almost 10% also reacted to placebo.[53] Similarly, in a small retrospective study of twenty adults with a history of benign rash, benign somatic symptoms, or unknown history associated with the last penicillin exposure of more than one year prior to assessment, none of the subjects developed immediate, or delayed hypersensitivity reactions.[54]

## E. DEFINING LOW RISK PATIENTS

It is crucial to define low-risk patients for true amoxicillin sensitivity as these patients are more likely to benefit from a direct drug challenge approach. A multicenter study in Australia found that the optimal definition for low-risk penicillin allergy history in patients 16 years or older is a benign rash, either immediate or delayed, occurring at least one year prior to evaluation.[55] In another U.S. study, patients five years or older with a cutaneous-only or unknown reaction (>1 year for those aged 5-17 years; >10 years for those 18 years or older) were randomized 1:1 to skin tests or a 2-step direct challenge. All children younger than five years of age (n=13) underwent direct challenge, and patients with extra-cutaneous reaction histories underwent skin tests. This study concluded that in those subjects aged 5 to 17 years old, low-risk patients included those with cutaneous reactions only that occurred at least one year prior to evaluation, while in those that were 18 years and older, low-risk patients were those reporting with cutaneous reactions only that occurred at least ten years prior to assessment.[56] Finally, another Australian study developed a statistical model to help define low-risk criteria for direct amoxicillin challenges.[57] This study defined patients with a total score less than 3 as low-risk with a negative predictive value of 96%. The major criteria comprising this risk score included an allergy event occurring five or fewer years ago (2 points) and anaphylaxis/angioedema or SCAR (2 points); the minor criterion (1 point), included whether treatment was required for an allergy episode.[57]

## F. CROSS-REACTIVITY

Beta lactam antibiotics belonging to the penicillin-class have an R1 side chain only. This R1 side chain is shared between penicillin and cephalosporin, as well as among cephalosporins and is thought to account for cross-reactivity based on a study demonstrating that structurally similar penicillins share IgE specificity.[58]

It has been reported that 2% of patients with positive reactions to multiple penicillin skin test reagents have sensitization to cephalosporins.[59] It has also been shown that patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, and cefatrizine) or receive them via rapid induction of drug tolerance.[60] It is noteworthy that cefazolin has a unique side chain and very low cross-reactivity with penicillin. There is no immunological or clinical cross-reactivity between penicillin and the monobactam aztreonam.[61]

There is evidence that allows for the safe use of all but a few early generation cephalosporins in patients with penicillin or amoxicillin allergy. Patients with a history of penicillin allergy generally have an elevated risk of allergic reaction and may develop an allergic response to cephalosporins by coincidence, but the risk is comparable to that of receiving a sulfonamide antibiotic.[61] Thus, the attributable risk of allergic cross-reactivity between penicillin and cephalosporins, for all but a few cephalosporins with similar side-chain structures to penicillin, is essentially nil.[61]

## F. CONCLUSION

Improving the diagnosis of amoxicillin hypersensitivity in children and reducing the risk of mislabeling is crucial. Until recently, the recommended allergy work-up to explore suspected allergic reactions to amoxicillin in children was based on data from adults and included skin tests and, if negative, a DPT.[4] However, given that pediatric studies have demonstrated the sensitivity of skin tests to be poor, false positive rates to be high, the positive predictive value low, and given that most reactions occurring during DPTs are mild, there has been

a recent paradigm shift in the diagnostic algorithm for benign skin reactions in favor of a direct DPT. The situation may differ in adults who are at higher risk for reactions, although some studies report favorable results in adults as well with the use of DPT.[53] Based on the published evidence to date, a DPT can be used in pediatric cases presenting with cutaneous non-vesicular lesions while more studies are required to establish the best diagnostic strategy in adults.


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