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How many suspected drug allergies in children are true allergies? A stepwise diagnostic evaluation from a single center

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ABSTRACT

Objective: The aim of this study was determine the rate of confirmed drug allergy using a stepwise diagnostic algorithm in children with a suspected or previously labeled drug allergy, to assess the proportion of patients in whom an incorrect drug-allergy label could be safely removed (delabeling rate), and to evaluate the diagnostic tests applied.

Materials and Methods: In this retrospective cross-sectional study, children presenting with suspected drug allergy to our pediatric allergy clinic between April 2023 and January 2025 were evaluated retrospectively. A stepwise protocol comprising detailed history, drug-specific IgE, skin tests (prick and intradermal), and drug provocation testing (oral or, when clinically indicated, subcutaneous or intravenous) was applied. Of 127 patients initially assessed, 41 were excluded and 86 who completed the clinically indicated diagnostic evaluation were analyzed.

Results: The mean age was 10.5±4.6 years. True drug allergy was confirmed in 16 patients (18.6%), whereas the incorrect drug-allergy label was safely removed in 70 (81.4%). Beta-lactams were the most common culprit group (12/16; 75.0%). Parental atopy, parental drug allergy, and personal atopy were significantly more frequent in the true-allergy group (p=0.004, p=0.028, and p=0.006, respectively), whereas no significant difference was found for age, sex, or laboratory parameters. In 10 confirmed patients, the diagnosis was established only by OPT. Anaphylaxis occurred in two of the 74 OPTs performed (2.7% per test).

Conclusion: In the majority of children presenting with suspected drug allergy, true allergy can be safely excluded through comprehensive diagnostic evaluation. Under appropriate patient selection and safe conditions, OPT is the gold-standard method for confirming or excluding true drug allergy, while specific IgE and skin tests support a stepwise evaluation for selected drugs; referral of these children to a pediatric allergist is important for both individual patient safety and antimicrobial stewardship.

Keywords: Anti-bacterial agents, beta-lactams, child, drug hypersensitivity, immunoglobulin E, skin tests

Introduction

Drug hypersensitivity reactions (DHRs) are dose-independent, unpredictable reactions that arise through immunological or non-immunological mechanisms and occur only in susceptible individuals (1). Frequently encountered in clinical practice, these reactions pose substantial diagnostic and management challenges, particularly in the pediatric population. Although the prevalence of drug allergy in childhood is reported to be high, a considerable proportion of these data rely on patient or parental reports and do not accurately reflect true immunological reactions confirmed by detailed allergological evaluation (2,3).

Recent studies have shown that the great majority of reported drug allergies cannot be confirmed after comprehensive diagnostic work-up (2,3). This indicates that the “drug-allergy label” is frequently applied incorrectly and over-diagnosed in clinical practice. Labels assigned in childhood in particular often persist throughout life and substantially restrict treatment options. Indeed, individuals carrying a drug-allergy label are frequently directed to more expensive, more toxic, or broader-spectrum alternative treatments, which both reduces treatment efficacy and increases the risk of adverse effects (4,5).

Incorrect drug-allergy labeling has important consequences not only at the individual level but also at the societal level. These include acceleration of antimicrobial resistance due to unnecessary antibiotic use, increased healthcare costs, and prolonged hospital stays (6,7). The widespread prevalence of incorrect allergy labels for beta-lactam antibiotics in particular further complicates clinical management by restricting the use of effective, narrow-spectrum treatment options (6-8).

Accurate diagnosis of DHRs is critical for preventing unnecessary labeling and determining appropriate treatment strategies. In this process, a detailed clinical history, in vitro tests (drug-specific IgE), and in vivo tests (skin prick and intradermal tests) play important roles, while the oral drug provocation test (OPT) is accepted as the gold-standard method (9-11). Performing OPT under safe conditions with

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appropriate patient selection constitutes a fundamental step in confirming true drug allergy and removing incorrect labels. In contrast, current data on the true frequency of DHRs in childhood and the clinical efficacy of diagnostic tests are limited, and data from our country in particular are scarce (12). This leads to a lack of standardization in the management of drug allergy in pediatric patients.

In this study, we aimed to determine the rate of true drug allergy by applying a stepwise diagnostic algorithm in pediatric patients who had been labeled as drug allergic at various outpatient clinics or referred to our clinic with suspected drug allergy, to determine the delabeling rate—the proportion of children in whom an incorrect drug-allergy label could be safely removed—and to demonstrate the clinical value of the diagnostic tests used (13).

Materials and Methods

Study design and population

This study was designed as a retrospective cross-sectional descriptive investigation. Patients who presented with suspected drug allergy to the pediatric immunology and allergy clinic of Şanlıurfa Training and Research Hospital between April 2023 and January 2025 were reviewed retrospectively. The records of all consecutive patients who presented with suspected drug allergy or who had previously been given a "drug-allergy label" at other centers were reviewed. Diagnostic tests were performed within routine clinical practice after obtaining patient/parental consent; ethics committee approval was obtained for the retrospective use of data.

Inclusion and exclusion criteria

Patients meeting the following criteria were included: pediatric patients (0-18 years) with a history of DHR or carrying a drug-allergy label; those who completed the diagnostic evaluation steps planned according to the suspected drug and clinical indication; and those able to attend the clinic regularly.

Patients were excluded in the following situations: those who declined to complete the diagnostic test protocol; those who were lost to follow-up and could not attend the stepwise testing program regularly; those for whom oral provocation testing was not performed because a reliable alternative drug was available; and those whose diagnostic evaluation could not be completed for any other reason. The number of patients at each stage, together with the reasons for exclusion, is reported in the Results and summarized in the patient flow diagram (Figure 1).

Diagnostic algorithm

A diagnostic protocol comprising applicable steps according to the suspected drug and clinical risk assessment was applied.

The diagnostic pathway was tailored to the suspected drug and to a risk assessment based on the index reaction. In line with current EAACI recommendations, patients were stratified as low or high risk according to the phenotype, severity, and timing of the index reaction (10,14,15). Low-risk reactions were defined as benign, delayed-onset cutaneous

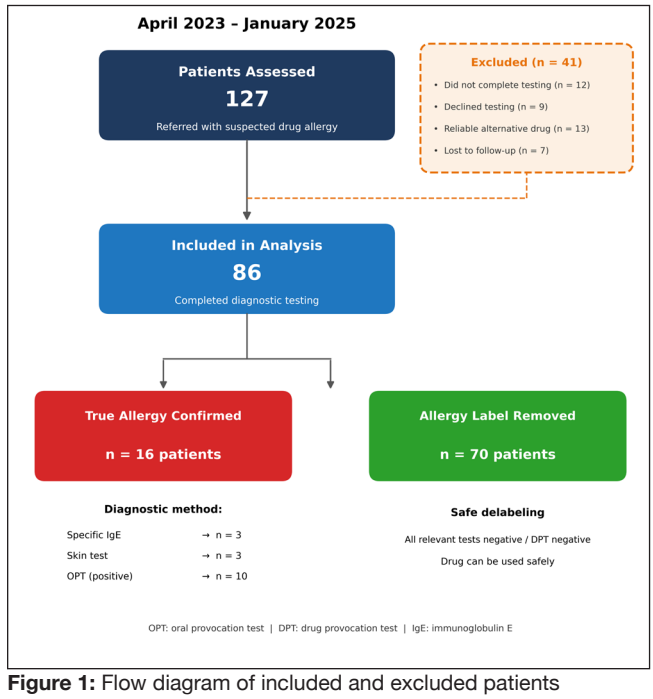


Figure 1: Flow diagram of included and excluded patients

manifestations without systemic involvement (e.g., a mild maculopapular exanthem or mild non-immediate urticaria) occurring in a child without significant comorbidity, whereas high-risk reactions included immediate-type reactions, anaphylaxis, severe or systemic reactions, and reactions suggestive of a severe cutaneous adverse reaction. For culprit drugs with validated test material—principally beta-lactams—drug-specific IgE and/or skin testing were performed before provocation in all patients for whom such testing was applicable. Patients proceeded directly to oral provocation testing, without prior skin testing, when no validated skin test or specific IgE was available for the culprit drug (e.g., non-steroidal anti-inflammatory drugs, macrolides, and antiepileptics) or when a low-risk reaction justified direct provocation, in accordance with current recommendations (10,14,15).

Step 1 – Detailed drug allergy history: The implicated drug, the time of reaction onset, clinical findings, the presence of concomitant disease, and atopic history were recorded using a standardized form.

Step 2 – In vitro tests: For the beta-lactam group, specific IgE levels for ampicillin, amoxicillin, penicillin V, and penicillin G were measured. A drug-specific IgE level of ≥0.35 kU/L was accepted as positive. Positive results were interpreted together with a clinically compatible reaction history. In patients with positive specific IgE, a diagnosis of beta-lactam allergy was made without further testing.

Step 3 – Skin tests: When specific IgE was negative or could not be measured, skin prick and intradermal (ID) tests were performed in accordance with the ENDA/EAACI guidelines (9,11,12). Skin tests were performed at the non-irritant drug concentrations recommended in the ENDA/EAACI position paper (9). For amoxicillin-clavulanate, test solutions were prepared at these non-irritant concentrations from the injectable (parenteral) formulation; because no separate test

material was available for clavulanic acid, discrimination between the amoxicillin and clavulanic acid components could not be made.

Step 4 – Oral drug provocation test (OPT): In patients with negative skin tests, in whom skin testing was not applicable, or who were classified as low risk, an open oral drug provocation test was performed under continuous medical supervision in a setting equipped for the management of anaphylaxis (9,10,15). In our protocol, the full age- and weight-appropriate therapeutic dose was administered in successive, increasing portions (approximately 20%, 30%, and 50% of the total dose) at 30-minute intervals, with observation for at least 2 hours after the final dose, consistent with current recommendations (15). When no immediate reaction occurred but a non-immediate (delayed) reaction was suspected from the index history, the drug was continued at therapeutic doses at home for 5 days, and the family was contacted by telephone to record any delayed reaction. A test was regarded as positive when objective, reproducible signs developed during or after provocation—such as urticaria, angioedema, erythema or a measurable exanthem, rhinoconjunctivitis, wheezing or dyspnea, laryngeal edema, gastrointestinal symptoms accompanied by objective findings, hypotension, or anaphylaxis—whereas isolated subjective symptoms in the absence of objective findings were not accepted as a positive result (10,15). If any systemic reaction developed, the test was terminated immediately and appropriate treatment was administered. Because no validated skin test or specific IgE was available for azithromycin, diagnostic evaluation in that patient was performed directly by OPT (10). Although provocation was performed orally in most patients, a non-oral route was used when appropriate for the drug: subcutaneous provocation for local anesthetics and graded intravenous provocation for parenterally administered drugs (ceftriaxone, amikacin, and paracetamol).

Definitions

Reactions were characterized both by the organ system(s) involved and by overall severity. Anaphylaxis was defined according to the EAACI and World Allergy Organization criteria as either (i) an acute reaction with involvement of the skin and/or mucosal tissue together with at least one of respiratory compromise, reduced blood pressure or associated end-organ symptoms, or severe gastrointestinal symptoms; or (ii) the acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient, even in the absence of typical skin involvement (16,17). For the description of organ-system involvement, each affected system was recorded separately, and patients who met the criteria for anaphylaxis were additionally counted in the anaphylaxis category. Consequently, a patient with multisystem involvement could be represented both under the relevant individual organ systems and under anaphylaxis, so the sum of organ-system counts may exceed the number of patients. Overall reaction severity was graded as mild, moderate, severe, or anaphylaxis.

Statistical analysis

Data were analyzed using SPSS v26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation (SD) or median (min-max); categorical variables were expressed as number and percentage (n,%). Normality of distribution was assessed with the Kolmogorov-Smirnov test. For between-group comparisons, the Student t-test or Mann-Whitney U test was used for continuous variables, and the chi-square or Fisher exact test for categorical variables. A p value <0.050 was considered statistically significant. Because a large number of variables were examined in the between-group comparisons, these analyses are exploratory (hypothesis-generating); no correction for multiple comparisons was applied, and the significant associations obtained should be interpreted with caution. For the categorical variables that differed significantly between the groups, unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the logit (Woolf) method. Multivariable logistic regression was not performed because only 16 outcome events were observed among three candidate predictors, resulting in approximately five events per variable. Simulation studies have suggested that a low number of events per variable may increase the risk of biased parameter estimates, inaccurate variance estimates, and inadequate confidence interval coverage. Therefore, multivariable analysis was considered unlikely to provide sufficiently reliable estimates (18). Penalized (Firth) approaches were also considered; however, with only 16 outcome events and three clinically inter-related predictors, the resulting estimates would remain too imprecise to support inference about independent effects, as is already apparent from the width of the univariable confidence intervals. The associations identified in the univariable comparisons are therefore reported as exploratory and hypothesis-generating.

Results

Patient flow

During the study period, 127 patients were assessed for suspected drug allergy. Of these, 41 (32.3%) were excluded: 12 whose diagnostic evaluation could not be completed, 9 who declined testing, 13 for whom oral provocation testing was not performed because a reliable alternative drug was available, and 7 who were lost to follow-up. The remaining 86 patients (67.7%) completed the full stepwise diagnostic protocol and were included in the analysis (Figure 1).

Demographic and clinical characteristics of the whole study group

The mean age of the 86 patients included was 10.5±4.6 years (range: 2-18 years); 41 were girls (47.7%) and 45 were boys (52.3%). A parental history of atopy was present in 25.6% (n=22) and a parental history of drug allergy in 12.8% (n=11). Among accompanying allergic diseases, asthma was found in 8.1% (n=7), allergic rhinitis in 11.6% (n=10), atopic dermatitis in 4.7% (n=4), and food allergy in 3.5% (n=3) (Table I).

The suspected drugs were most frequently antibiotics (n=64; 68.1%), followed by non-steroidal anti-inflammatory drugs (NSAIDs; n=25; 26.6%), local anesthetics (n=3; 3.2%), and antiepileptics (n=2; 2.1%). The most frequently suspected antibiotic group was beta-lactams (n=47), and the most frequently suspected NSAID/analgesic agent was paracetamol (n=19); paracetamol, a weak COX-1 inhibitor, was evaluated within the NSAID/analgesic group in accordance with the

Table I: Demographic, clinical, and laboratory characteristics of the study group and comparison according to confirmed drug allergy status

Variable	Total	Confirmed drug allergy	Allergy excluded	p
Total number of patients	86	16	70	-
Age (years)*	10.5±4.6 (2-18)	10.2±5.0	10.6±4.5	0.772
Sex - female†	41 (47.7)	7 (43.8)	34 (48.6)	0.787
Parental history of atopy†	22 (25.6)	9 (56.2)	13 (18.6)	0.004
Parental drug allergy†	11 (12.8)	5 (31.2)	6 (8.6)	0.028
Personal atopy†	19 (22.1)	8 (50.0)	11 (15.7)	0.006
Comorbid asthma†	7 (8.1)	3 (18.8)	4 (5.7)	0.116
Comorbid allergic rhinitis†	10 (11.6)	4 (25.0)	6 (8.6)	0.085
Comorbid atopic dermatitis†	4 (4.7)	2 (12.5)	2 (2.9)	0.156
Comorbid food allergy†	3 (3.5)	1 (6.3)	2 (2.9)	0.465
Absolute eosinophil count (/mm³)*	364±238 (0-1350)	380±240	360±235	0.766
Eosinophil (%)‡	4.7±2.3 (0-16.8)	5.0±2.4	4.6±2.2	0.138
Total IgE (IU/mL)‡	310±197 (1-1103)	325±205	307±195	0.236

**: mean±SD (min-max) (Student t-test), †: n (%) (chi-square or Fisher exact test), ‡: mean±SD (min-max)(Mann-Whitney U test)*

Table II: Clinical characteristics of the 16 patients with confirmed drug allergy

Patient	Culprit drug (group)	Sex / Age	Atopy (parental / personal)	Presenting reaction (onset)	Diagnostic test	Reaction during test / outcome
P1	Amoxicillin-clavulanate (beta-lactam)	F / 12	Yes / Asthma	Urticaria at hour 3	Sp IgE / Skin / OPT	Anaphylaxis during OPT
P2	Amoxicillin-clavulanate (beta-lactam)	M / 8	No / —	Angioedema at hour 2	Skin / OPT	MPE at min 10 of OPT
P3	Valproic acid (antiepileptic)	M / 11	No / —	Maculopapular exanthem at hour 3	OPT	Transient maculopapular rash during OPT
P4	Amoxicillin-clavulanate (beta-lactam)	F / 16	No / Asthma	Urticaria at hour 3	Sp IgE	Sp IgE positive (skin test and OPT not performed)
P5	Amoxicillin-clavulanate (beta-lactam)	F / 13	Yes / Allergic rhinitis	Urticaria at hours 3-4	Sp IgE / Skin / OPT	Urticaria during OPT
P6	Amoxicillin-clavulanate (beta-lactam)	M / 17	Yes / Urticaria	Urticaria + angioedema at hour 2	Sp IgE / Skin	Urticaria on ID test (OPT not performed)
P7	Ibuprofen (NSAID/analgesic)	M / 3	Yes / Atopic dermatitis	Urticaria at hour 2	OPT	Anaphylaxis at step 1 of OPT
P8	Amoxicillin-clavulanate (beta-lactam)	M / 5	No / —	Maculopapular exanthem at hour 2	Sp IgE / Skin / OPT	MPE at min 20 of OPT
P9	Penicillin (beta-lactam)	F / 17	Yes / Allergic rhinitis	Syncope at min 15	Sp IgE / Skin	Prick test positive (OPT not performed)
P10	Amoxicillin-clavulanate (beta-lactam)	F / 11	Yes / Allergic rhinitis, food allergy	Angioedema at hour 3	Sp IgE	Sp IgE positive (OPT not performed)
P11	Paracetamol + Penicillin (NSAID/ analgesic + beta-lactam)	M / 13	No / —	Urticaria at hour 5 / urticaria on day 1	Sp IgE / Skin / OPT	MPE at min 15 of OPT with paracetamol; urticaria at step 2 of OPT with penicillin
P12	Amoxicillin-clavulanate (beta-lactam)	F / 17	No / Allergic rhinitis, asthma	Angioedema at hour 4	Sp IgE	Sp IgE positive (OPT not performed)
P13	Ampicillin-sulbactam (beta-lactam)	M / 4	Yes / Atopic dermatitis, food allergy	Urticaria at hour 1	Sp IgE / Skin	Positivity on ID test (OPT not performed)
P14	Paracetamol (NSAID/analgesic)	M / 4	Yes / —	Urticaria at min 30	OPT	Urticaria at first dose of OPT
P15	Cefixime (beta-lactam)	F / 6	No / —	Urticaria at hour 2	OPT	Urticaria at min 30 of OPT
P16	Azithromycin (macrolide)	M / 7	Yes / —	Urticaria at hour 1	OPT	Urticaria at min 45 of OPT

***Sp IgE:** drug-specific IgE, **OPT:** oral provocation test, **ID:** intradermal, **MPE:** maculopapular exanthem/rash, **M:** male, **F:** female. In patient P11, two different drug allergies were confirmed in the same patient*

EAACI classification of hypersensitivity to NSAIDs (19). Because 8 patients had a history of allergy to more than one drug, the drug-group percentages given above were calculated over the total number of drug records (n=94). In 75 patients (87.2%), the reaction had developed within the first 6 hours; the most frequently affected system was the skin (90.7%, n=78), with respiratory involvement in 3 patients, gastrointestinal in 2, cardiovascular in 2, and anaphylaxis in 2 (because more than

Table III: Distribution of culprit drug groups in patients with confirmed drug allergy

Drug group	n (%)
Beta-lactam (alone)	11 (68.8)
NSAID/analgesic (alone)	2 (12.5)
Beta-lactam + NSAID/analgesic (P11)	1 (6.3)
Antiepileptic	1 (6.3)
Macrolide	1 (6.3)
Total	16 (100)

In patient P11, both beta-lactam and NSAID/analgesic allergy were confirmed, so this patient is included in two groups; therefore, the patient-based total is 16 while the number of confirmed allergens/drugs is 17. All beta-lactam-involving cases: 12/16 (75.0%).

one system was affected in some patients, the sum of system counts exceeds the number of patients).

Rate of true drug allergy

As a result of the stepwise diagnostic evaluation, true drug allergy was confirmed in only 16 of the 86 patients (18.6%); the incorrect drug-allergy label was safely removed in the remaining 70 patients (81.4%). A total of 203 diagnostic tests were performed: 56 specific IgE tests, 59 skin tests (prick and intradermal), and 88 drug provocation tests (DPTs), of which 74 were oral (OPT), 3 subcutaneous, and 11 graded intravenous. By diagnostic method, 3 patients were diagnosed by positive specific IgE (beta-lactam allergy; P4, P10, P12), 3 patients by positive skin test (beta-lactam allergy; P6, P9, P13), and 10 patients by positive oral provocation (beta-lactam alone in 5, NSAID/analgesic alone in 2, antiepileptic in 1, macrolide in 1, and both beta-lactam and NSAID/analgesic in 1 [P11]). For culprit drugs without a validated in vitro or skin test (NSAIDs/analgesics, non-beta-lactam antibiotics, and antiepileptics) or in the case of a low-risk reaction, 52 of the 88 provocations were performed directly, without prior specific IgE or skin testing (25 NSAID/analgesic, 16 non-beta-lactam antibiotic, 2 antiepileptic, and 9 low-risk beta-lactam). Thus, only a minority of the diagnostic work-up served to establish a true allergy, whereas the large majority served to safely exclude it and remove the incorrect label.

In patients evaluated for a suspected non-immediate reaction who had a negative in-hospital oral provocation, the culprit drug was continued at home for 5 days; no additional delayed reactions were reported during this period.

Characteristics of the 16 patients with confirmed allergy

The mean age of the 16 patients with confirmed true drug allergy was 10.2±5.0 years (median: 11.0; range: 3-17 years). The distribution by age group was: ≤5 years, 4 patients (25.0%); 6-11 years, 5 patients (31.2%); and 12-18 years, 7 patients (43.8%). A parental history of atopy was present in 9 patients (56.2%) and a personal atopic disease in 8 patients (50.0%). When reaction severity was assessed, anaphylaxis was observed in 2 patients (12.5%), a severe reaction in 1 (6.3%), a moderate reaction in 8 (50.0%), and a mild reaction in 5 (31.2%) (Table II).

Distribution of culprit drug groups

The distribution of culprit drug groups among the 16 patients with confirmed allergy is presented in Table III. Beta-lactams accounted for the majority of confirmed allergies (Table III).

Comparison of groups with and without drug allergy

When the groups with confirmed (n=16) and excluded (n=70) drug allergy were compared, a parental history of atopy, a parental history of drug allergy, and the presence of personal atopy were significantly higher in the true drug allergy group (p=0.004, p=0.028, and p=0.006, respectively). The corresponding unadjusted ORs were 5.64 (95% CI 1.77-17.93) for a parental history of atopy, 4.85 (95% CI 1.26-18.67) for a parental history of drug allergy, and 5.36 (95% CI 1.66-17.32) for personal atopy; the width of these intervals reflects the small number of patients with confirmed allergy. No significant difference was found with respect to age, sex, asthma, allergic rhinitis, atopic dermatitis, food allergy, absolute eosinophil count, eosinophil percentage, or total IgE level (Table I).

Discussion

Our study demonstrated that the great majority (81.4%) of children evaluated for suspected drug allergy did not in fact have a drug allergy. This rate is consistent with the global literature; although approximately 10% of parents report suspected drug allergy in their children, confirmation rates of true allergy after comprehensive evaluation generally remain between 1% and 20% (12,13,20). Indeed, the prevalence of confirmed drug allergy in the general pediatric population has been shown to be approximately 0.05%, and only a small proportion of reported drug reactions can be confirmed by comprehensive testing (21,22).

One of the most original findings of our study is that a parental history of atopy, a parental history of drug allergy, and the presence of personal atopy were significantly higher in the true-allergy group.These findings suggest that these three parameters may be associated with true drug allergy. However, these odds ratios are unadjusted; because the three characteristics are clinically inter-related and only 16 patients had confirmed allergy, we could not determine whether any of them is an independent predictor. Given the limited sample size (n=16), the wide confidence intervals, and the large number of comparisons, these associations are hypothesis-generating and require confirmation in larger, prospectively designed studies. Nevertheless, the absence of a significant difference between the two groups in terms of age, sex, laboratory values, and other clinical parameters suggests that drug-allergy decisions based solely on history and laboratory parameters may be insufficient, and supports the importance of the stepwise diagnostic algorithm and especially OPT (9-11).

Beta-lactams stood out as the most frequent cause of true allergies; calculated per patient, beta-lactam allergy was confirmed in 12/16 (75.0%) cases (21,203). This finding is consistent with the international literature showing that the majority of drug allergies reported in children are attributed to beta-lactams (12,24). Nevertheless, it is known that up to 90% of beta-lactam allergy labels are incorrect; this arises particularly from the frequent interpretation of maculopapular rashes accompanying infection in children as beta-lactam allergy (11,24). In patient P11, the simultaneous confirmation of both penicillin and paracetamol allergy demonstrates that

each suspected drug must be evaluated separately in cases of multiple-agent sensitization (10).

In the diagnostic process, OPT played a key role both in confirming and in safely excluding drug allergy; in 10 of the patients with confirmed true allergy, the diagnosis could be established only by OPT. Current literature showing that direct OPT can be safely applied in children with mild symptoms and negative skin test results supports our approach (14). Because no validated skin test or specific IgE was available for azithromycin, diagnostic evaluation was performed directly by OPT and the reaction was confirmed; this once again demonstrates the importance of developing a separate diagnostic protocol for each agent (10). In the NSAID group, ibuprofen and paracetamol allergies could be proven only by OPT; the diagnostic value of specific IgE and skin tests for these drugs is quite limited, and OPT remains the primary approach (22,23).

Anaphylaxis occurred in two of the 74 OPTs performed in our study (2.7% per test), underscoring that these tests must be conducted only by an experienced team with full resuscitation facilities available (9,10). Because of the small denominator and the inclusion of different drug classes and risk profiles, this center-specific rate should be interpreted with caution and not directly compared with cohorts limited to low-risk beta-lactam challenges. Both anaphylaxis episodes were promptly recognized and successfully treated in a center equipped for resuscitation, and the patients were safely discharged; this supports the view that, when performed under appropriate patient selection and safe conditions, OPT is a reliable diagnostic method. Removing an incorrect drug-allergy label not only enhances individual patient safety but also, by enabling the use of first-line antibiotics, both reduces antimicrobial resistance and contributes to health economics (6-8).

Limitations

This study should be interpreted in light of the following limitations:

- Retrospective cross-sectional design: Data were obtained retrospectively from patient records, which entails the possibility that some clinical information was recorded in a non-standardized or incomplete manner and does not permit causal inference.
- Single center: The study is based on data from a single center. Because our hospital is a regional referral center, more severe and complex cases may have presented preferentially, which may have made the proportion of patients with confirmed allergy appear relatively high compared with the general population.
- Sample size: Because the study had a retrospective cross-sectional design, a prospective power analysis could not be performed before data collection. Nonetheless, the sample of 86 patients is comparable to the sample sizes reported in international single-center studies on this subject (30–120 patients) (12,13,20,25). The relatively limited number of patients with confirmed true drug allergy (n=16) restricts the statistical power of subgroup analyses in particular, so these findings should be confirmed in larger, prospectively designed studies.
- Limited in vitro test infrastructure for non–beta-lactam drugs: The lack of validated specific-IgE and skin-test protocols for NSAIDs, macrolides, and antiepileptics made the diagnostic process for these drugs largely dependent on OPT, raising the possibility that some cases in which a skin test could theoretically have been positive were missed.
- Absence of long-term follow-up data: Long-term follow-up data on whether delabeled patients subsequently tolerated the relevant drugs are not available.
- Exclusion of patients for whom an alternative drug was available: In 13 patients, provocation testing was not performed because a reliable and effective alternative agent was available and the culprit drug was not immediately required; considering the small but real risk of provocation, these patients were not challenged and were therefore not delabeled. This represents a pragmatic, risk-based clinical decision intended to avoid unnecessary provocation in children who did not need the specific drug. We nevertheless acknowledge that the availability of an alternative is not, in itself, a sufficient reason to forgo provocation, since confirming or excluding a suspected allergy has value independent of current treatment options and the label may persist throughout life. As these patients were not part of the analyzed cohort and retained an unverified drug-allergy label, we recognize this as a limitation: it may introduce a degree of selection bias and limits the generalizability and completeness of delabeling, although it does not alter the calculations performed within the analyzed cohort of 86 patients.

Multicenter, prospective studies with larger samples are needed to address these limitations.

Conclusion

In the great majority (81.4%) of pediatric patients presenting with suspected drug allergy, true drug allergy can be excluded through comprehensive diagnostic evaluation. History, clinical findings, and basic laboratory parameters alone were insufficient to predict the patient with true allergy; in contrast, a parental history of atopy, a parental history of drug allergy, and the presence of personal atopy were higher in the true-allergy group, although prospective studies are needed to confirm these associations. For confirming or safely excluding true drug allergy, OPT—under appropriate patient selection and safe conditions—is the principal diagnostic method and gold standard, while specific IgE and skin tests support a stepwise evaluation for selected drugs. Structured evaluation and, when clinically appropriate, referral of children with suspected drug allergy to a pediatric allergist will benefit both individual patient safety and antimicrobial stewardship at the societal level (4,5,26).

Presented

Preliminary results of this study, based on a smaller sample, were presented as an oral presentation at the 59th Turkish Pediatric Congress (Türk Pediatri Kongresi, TPK), held on 22–26 May 2024 in the Turkish Republic of Northern Cyprus.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Harran University (27.01.2025, reference number: HRÜ/25.02.43).

Contribution of the authors

Study conception and design: MŞK; data collection: MŞK, APS; analysis and interpretation of results: MŞK, APS; draft manuscript preparation: MŞK, APS. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

Generative AI Statement

During the preparation of this manuscript, the authors used a generative AI-assisted tool (ChatGPT, OpenAI) in August 2026 for English-language checking, the correction of spelling and typographical errors, formatting, and preparation of the flow diagram (Figure 1). No AI-assisted tool was used for data collection, statistical analysis, interpretation of results, or the generation of original scientific content. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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