

# DON'T WE OVERESTIMATE DRUG ALLERGIES IN CHILDREN?

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## Abstract

**Objectives:** On average about 10% of parents report hypersensitivity to at least 1 drug in their children. After diagnosis process a few of these reactions are being confirmed as drug hypersensitivity reactions. The aim of the study was to assess the real-life prevalence of drug hypersensitivity in children based on drug provocation tests. **Material and Methods:** The authors included 113 children, aged 4–18 years, referred to Pediatrics and Allergy Clinic in Łódź, Poland, due to incidence of adverse reaction during treatment. Medical history regarding allergies to drugs was taken in accordance to the form developed by the United States Food and Drug Administration Adverse Event Reporting System. Skin prick tests, intradermal test and drug provocation test were performed in all patients. **Results:** In all 113 patients suspected of drug allergy, after all diagnostic procedures, the authors proved IgE-mediated allergy to  $\beta$ -lactams, nonsteroid anti-inflammatory drugs, local anesthetics in 19 patients (16.8%). Previous history of allergy was a risk factor for drug allergy in studied patients ( $p = 0.001$ ). The most frequent symptoms of allergy were urticaria and erythematous papular rash. **Conclusions:** Drug allergy is a difficult problem in the practice of a doctor and is difficult to diagnose, especially in the pediatric population. It seems that too often isolated symptoms reported during infection or disease are taken as a symptom of drug allergy, and not as a symptom resulting from the course of the disease. *Int J Occup Med Environ Health. 2023;36(5):632–42*

## Key words:

local anesthetics, hypersensitivity, drug allergy, children, nonsteroidal anti-inflammatory drugs,  $\beta$ -lactam antibiotics

## INTRODUCTION

World Health Organization has defined an adverse drug reaction in adults and children as “any harmful, unintended and undesired effect of a drug that occurs at doses used for treatment, prevention or diagnoses” [1]. Larger part of these reactions are categorized as A type reactions which are describes as predictable, common, usually dose-dependent and caused by previously known pharmacological characteristics of the drug and its side effects [1–3]. Reactions due to allergy to a drug are categorized as type B reactions which are supposed to be independent of dose and affect a small population, which suggests that individual patient factors are important here [2].

Drug hypersensitivity reactions (DHRs) can be immediate and nonimmediate reactions. Usually immediate reactions appear within minutes to 1 h after drug administration and they are linked with direct mast cell activation or IgE-mediated reaction. [4]. Concerning the symptoms, immediate reactions clinically can be observed as urticaria and angioedema, rhinitis, eye symptoms (redness and itching), abdominal pain, nausea, vomiting, loose stools, but also as severe respiratory symptoms and anaphylaxis [2,4]. Nonimmediate reactions develop after  $\geq 1$  h after drug administration and usually are linked with complement activation, T-cell mediated response or production of antigen-specific IgG [2,4]. Delayed reactions start usu-

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ally after 1 to several hours after drug administration and include maculopapular exanthema, eczema or delayed urticaria. However severe delayed reactions can also be observed even weeks after drug administration and include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug eruption with eosinophilia and systemic symptoms (DRESS), but also hemolytic anemia, cytopenia, hepatitis vasculitis and et cetera [2,4].

Data on prevalence of drug allergy among juvenile patients is limited. On average about 10% of parents report suspected allergy to  $\geq 1$  drugs in their children [5–7]. This may affect quality of life, but also leads to avoiding the drug suspected for adverse drug reaction and use of suboptimal, often more expensive one. Never the less after allergy diagnosis a few of these reactions are being confirmed as drug hypersensitivity reactions. In pediatric population the most cases of reported drug hypersensitivity concerns  $\beta$ -lactam antibiotics (BLAs), next nonsteroidal anti-inflammatory drugs (NSAIDs) and finally non- $\beta$ -lactam antibiotics (nBLAs) and anesthetic drugs [2,4,5]. The symptoms usually linked with drug allergy vary with age from maculopapular and non-immediate exanthemas in younger children to immediate urticaria, angioedema and other life threatening reactions in adolescent [5,6,8–12]. Different drugs use different mechanism to result in hypersensitivity.

According to the statement of European Network for Drug Allergy (ENDA) and Drug Allergy Interest Group of the European Academy of Allergy and Clinical Immunology (EAACI) diagnosing drug hypersensitivity reaction (DHR) there are no different algorithms for children and adults [5]. However performing skin prick tests and especially intradermal tests seems to be more difficult in small children as these are painful and inadequate.

The study aimed to assess the real-life prevalence of drug hypersensitivity in children referred to the authors' Allergy Clinic after an incidence of adverse event during treatment verified by drug provocation tests.

## MATERIAL AND METHODS

### Patients

The authors included all 113 children, aged 4–18 years, referred to Pediatrics and Allergy Clinic in Łódź, Poland due to incidence of adverse reaction during treatment in the last 6 months, diagnosed by a pediatrician as possible allergic reaction. Demographic characteristics and medical history were recorded and analyzed. Drug hypersensitivity reactions were reported during or after treatment with BLAs, NSAIDs, nBLAs, local anesthetics (LAs) or anesthetics used for premedication for general anesthesia. Medical history regarding allergies to drugs and drugs used was taken in accordance with the form developed by the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Immediate reactions were considered as reactions with appearance of clinical symptoms within 1 h after drug intake [2]. Reactions with onset  $> 1$  h after the last intake but  $\leq 24$  h were considered as delayed; reactions  $> 24$  h from the last drug intake were defined as late.

The study was conducted in March 2018–February 2022. It was approved by the Medical Ethics Committee of the Medical University of Lodz (RNN/147/18/KE). All parents or legal guardians gave their oral and written consent for the evaluation of data from medical documentation of their children.

All patients were advised to stop antihistamine drugs intake at least 14 days before the diagnostic procedures and also all of them were examined by an medical doctor in order to exclude on-going infection or skin changes which could potentially make difficulties in symptoms interpretation during the provocation test. For clarity, patients with chronic diseases requiring a prolonged drug intake were not included.

During diagnosis following tests were applied.

### Skin prick tests

A skin prick tests (SPT) carried out according to the general recommendations for skin prick tests procedures [13]

were done by pricking the skin percutaneously with a prick needle through an allergen solution (drug), positive (histamine phosphate 10 mg/ml) and negative (saline buffer/50% glycerol) controls. Assessment of the tests was done after 15–20 min of application; a positive result was defined as a wheal  $\geq 3$  mm diameter. Concentrations used for skin prick test were prepared according to ENDA/EAACI Allergy Interest Group [14].

### Intradermal skin tests

Intradermal skin tests were performed using the Mantoux technique. A wheal with erythema and diameter  $\geq 3$  mm compared to the negative control was assessed as positive. Concentrations used for intradermal tests were prepared according to ENDA/EAACI Drug Allergy Interest Group [14].

### Specific IgE

For BLA allergy IgE specific antibodies were assessed for amoxicillin, amoxicillin/clavulanic acid, cefuroxime, ceftriaxone using Polycheck Allergy (Biocheck GmbH, Münster, Germany). The Polycheck® Screening Assay is an enzyme immunoassay for the quantitative measurement of allergen-specific IgE in serum. For NSAIDs and nBLAs serum-specific IgE were unavailable.

### Drug provocation test

Considering the fact that the investigated population consisted of children with big difference in weight and to unify the threshold dose different protocols for BLA, nBLA and NSAIDs were used [9,15,16]. The protocols for BLA and nBLA were based on described by Chiriac et al. [15] 4 steps: 5%–15%–30%–50% of the therapeutic dose of drug. Daily therapeutic dose was calculated as follows: for amoxicillin 50 mg/kg, cefuroxime 30 mg/kg, claritromycin 15 mg/kg. For NSAIDs drug provocation test (DPT) protocols described by Zambonino et al. [16] were used – 3 steps: 1/4, 1/4 and 1/2 of cumulative dose (paracetamol 15 mg/kg/dose; ibuprofen 10 mg/kg).

For acetylsalicylic acid (ASA) protocol developed by Nizankowska et al. [17] was used.

Each DPT lasted 2 days: 1 day placebo only, and 1 day drug testing. Subsequent doses were administered every hour and between the fifth and the sixth dose the time interval was 8 h in order to imitate the dosage in case of need.

Before each dose placebo/DPT vital signs (heart rate, blood pressure and spirometry when appropriate) were performed. The DPT was defined as positive if objective signs appeared during drug administration. In all cases subjective symptoms appeared, the physician leading the test could decide whether to repeat the last dose or to divide next dose in 2 steps. When patient reported subjective symptoms but completed the DPT without objective signs, DPT was described as negative. If a patient had objective symptoms at any stage, the DPT was considered positive, discontinued, and appropriate treatment was initiated.

According to ENDA/EAACI Drug Allergy Interest Group recommendations for DPT indications the authors performed DPT after assuring all safety measures (intravenous access, emergency set) in case of anaphylaxis during DPT [15]. Disposable capsules with the considered preparation prepared by the hospital pharmacy in accordance with the principles of asepsis and antiseptics were used for the DPT.

### Statistical analysis

Categorical variables were described by integer numbers and percentages. Numerical features were depicted with their mean, median, standard deviation and minimum-maximum values. The Pearson's  $\chi^2$  test of independence was conducted for descriptive purposes between the groups. A binary logistic regression model was carried out in order to estimate adjusted odds ratios for clinical conditions, controlling for age, gender and BMI. A level of  $p < 0.05$  was considered statistically significant. All the statistical procedures were performed using Statistica v. 14 (TIBCO Software Inc., Palo Alto, CA, USA).

## RESULTS

The current analysis is restricted to 113 children who underwent full diagnosis of suspected drug allergy. Baseline characteristics are given in Table 1.

In all 113 patients suspected of drug allergy, after all diagnostic procedures, IgE-mediated allergy (to BLAs, NSAIDs, LAs) in 19 patients (16.8%) was proved. Detailed data on the diagnosis of allergies in individual drug groups are presented in Table 2.

**Table 1.** Baseline characteristics of the study cohort of patients aged 4–18 years, March 2018–February 2022, Pediatrics and Allergy Clinic, Łódź, Poland

Variable	Participants (N = 113)
History of allergy [n (%)]	55 (48.7)
Gender [n (%)]	
female	50 (44.2)
male	63 (55.8)
Age [years]	
M±SD	9.9±4.4
Me (min.–max)	9.0 (4–17)
Pharmaceutical form [n (%)]	
tablets or capsules	38 (33.6)
suspension or syrup	48 (42.5)
other (e.g., topical, <i>i.m.</i> , <i>s.c.</i> , <i>i.v.</i> )	27 (23.9)
Severity [n (%)]	
anaphylactic shock	8 (7.1)
swelling of the lips and face, hives ( <i>urticaria</i> ), shortness of breath	87 (77.0)
small-lumped rash	18 (15.0)
Time of reaction [n (%)]	
immediate	50 (44.3)
delayed	39 (34.5)
late	24 (21.2)
Medical verdict on allergy (provocation test result) [n (%)]	
allergy confirmed	19 (17.1)
allergy ruled out	92 (82.9)

\* Missing data were case-wise deleted if applicable.

## BLA

In studied group 42 patients suspected of allergy to BLA were investigated. Among these patients the most common symptoms suggestive of allergy were urticaria and angioedema followed by erythematous papular rash. Severe anaphylaxis and anaphylactic shock have been observed less frequently (Table 3). In studied group IgE-mediated allergy to BLA was proved in 14.3% of patients (N = 6).

## NSAIDs

In studied group 42 patients suspected of allergy to NSAIDs were investigated. Among these patients the most common symptoms suggestive of allergy were urticaria and angioedema, less often erythematous papular rash. Severe anaphylaxis and anaphylactic shock have been observed least frequently (Table 3).

In the studied group allergy to NSAIDs was confirmed in 26.2% (N = 11) of studied patients.

## LAs

In studied group 23 patients suspected of allergy to LAs were investigated. Among these patients the most common symptoms suggestive of allergy were urticaria and angioedema, less often erythematous papular rash. The authors did not observe any severe anaphylaxis after administration of LAs (Table 3).

In the patients suspected for allergy to LAs investigated in this study, after performing all diagnostic procedures allergy was proved just in 2 patients.

Previous history of allergy was a risk factor for drug allergy in studied patients (p-value 0.001) (Table 2).

The predictive validity indicators of provocation diagnostic test were as follows: sensitivity (29.6%), specificity (94.7%), positive predictive value (84.2%), negative predictive value (58.7%), disease prevalence (48.7%). The authors also did not find differences between gender and incidence of drug allergy.

**Table 2.** Clinical confirmation of drug allergy in the studied patients aged 4–18 years by pharmaceutical agent and former history of allergy, March 2018–February 2022, Pediatrics and Allergy Clinic, Łódź, Poland

Variable	Provocation test result			P
	positive [n (%)]	negative [n (%)]	total [n]	
Drugs	19 (16.8)	94 (83.2)	113	0.465
antibiotics				
β-lactam	6 (14.3)	36 (85.7)	42	
other	0 (0.0)	6 (100.0)	6	
nonsteroidal anti-inflammatory drugs	11 (26.2)	31 (73.8)	42	
local anesthetics	2 (8.7)	21 (91.3)	23	
History of allergy	19 (17.1)	92 (82.9)	111	<b>&lt;0.001</b>
yes	16 (29.6)	38 (70.4)	54	
no	3 (5.3)	54 (94.7)	57	

Bolded is p-value clinically significant if <0.05.

**Table 3.** Types of symptoms among groups of drugs suspected of causing allergies in patients aged 4–18 years, March 2018–February 2022, Pediatrics and Allergy Clinic, Łódź, Poland

Drugs	Symptom [n (%)]		
	anaphylactic shock	urticaria/angioedema	erythematous papular rash
Beta-lactam antibiotics	3 (7.14)	28 (66.67)	11 (26.2)
Nonsteroidal anti-inflammatory drugs	2 (4.76)	31 (73.8)	9 (21.42)
Local anesthetics	0	20 (87)	3 (13)

The discussed occurrence of drug allergy in the study participants was not associated with the pharmaceutical form of the drugs administered ( $p = 0.927$ ). The history of allergy was reported by 17 patients having ingested tablets (44.7%) vs. 21 individuals having taken suspensions or syrups (43.75%). The performed analysis showed no clinical relationship depending on age, sex and BMI.

## DISCUSSION

In adults, most of adverse drug reactions are type A reactions (about 80% of cases) and others are classified as B type reactions [18]. In children it seems to be the opposite – 10–15% of cases are thought to be linked with adverse drug reactions type A [18]. The major causes of drug

hypersensitivities in children concerns BLAs, followed by NSAIDs [7,19]. In pediatric population cutaneous symptoms, especially maculopapular eruptions are the most frequently reported symptoms [7,20,21]. Although diagnostics in 113 children referred to the authors' clinic "labelled" as allergic to a drug were performed, after drug provocation test only 19 cases of allergy (16.8%) were confirmed. Other reactions were non-specific, most probably linked with the main course of the disease.

## BLAs

In studied group IgE-mediated allergy to BLAs was proved in 14.6% of patients ( $N = 6$ ). These results are consistent with findings of other researchers stating that drug allergy and

especially antibiotic allergy is overreported [7,22,23]. Ponvert et al. [24] report in their study based on long term experience that only 15.9% of 1431 children with suspected allergy to BLAs were proved to be allergic. Similar results were reported by Caubet et al. [26] and Zambonino et al. [16] where respectively just 6.8% and 7.9%, of children diagnosed for drug allergy had positive drug provocation test. In both researches >700 children were investigated.

Amoxicillin is the most common cause of adverse reactions [27,28]. This is also the most common prescribed antibiotic in pediatric population as penicillins are the first choice therapy in most pediatric respiratory infections according to many guidelines [29–32]. More than 70% of children with viral infection is being given empirically antibiotic treatment (mostly with amoxicillin) [7,18,25,26]. Cutaneous reaction as maculopapular eruptions that are secondary to that condition and are often considered as adverse drug reaction [27,33,34]. Caubet et al. state that 69.5% of cases where drug allergy diagnostics was triggered due to benign skin rash was actually a result of viral infection [26].

As many children are improperly “labelled” as allergic to BLAs a lot of researches underline the need of precise classification of penicillin allergy and also the need of detailed and validated allergic diagnostics [2,7,18,35]. An interesting questionnaire was proposed by Vyles et al. [35] on the basis of which a patient can be classified as “low-risk” or “high-risk” for penicillin allergy. They state that all patients in their study ranged as low-risk had no true penicillin allergy. Many studies have shown skin prick tests with BLAs before administration were useful in increasing the use of BLAs even in patients with self-reported penicillin allergy [36,37]. What is more Raja et al. [38] proved that skin prick test in emergency room for adults are very helpful in deciding to use antibiotics in a patient with an unclear history of allergy to BLAs. Of course it is important to underline that in patients with moderate to high risk of BLAs allergy and immediate reactions skin prick test are

supposed to be just an introduction to detailed diagnostics of allergy and only drug provocation test can “label” or “unlabel” the patient as allergic or not. According to guidelines it is recommended to preform skin prick tests with minor and major determinants, however these are not routinely available [39]. According to ENDA skin prick test can be performed with amoxicillin and different cephalosporins and recommendations for its concentrations in skin prick test performing have been proposed [14]. Their high negative predictive value in adults was assessed as 98% for penicillin but not for amoxicillin [40,41]. In pediatric population studies have shown that positive predictive value of skin testing is weak with the range of 20% [42]. Taking into account that skin testing is distressing and cumbersome to implement in younger children and in context of the results of several studies evaluating drug provocation test with skipping skin testing in children with history of immediate reactions to penicillins showing this as safe, the role of skin prick test as a single diagnostic tool is very little [43–46]. Up to this date drug provocation test remain the golden standard for diagnosis for drug allergy, however according to American Academy of Allergy, Asthma and Immunology and World Allergy Organization have recommended that “drug provocation test should be considered without prior skin testing in children with mild nonimmediate reactions to penicillins”[47,48].

### NSAIDs

Nonsteroidal anti-inflammatory drugs are the most frequently given drugs in infection as pain-killers, anti-inflammatory or antipyretic drugs [7,49]. In adult patients the prevalence is based mainly on aspirin intolerance, which is not common used in pediatric patients up to 12 years due to probable appearance of Reye's syndrome. The prevalence of NSAIDs hypersensitivity is reported 2–6% in general population, however exact data concerning children is lacking [50]. Nevertheless in many studies NSAIDs are pointed as a second culprit



group [3,5,7]. In the studied group the authors confirmed allergy to NSAIDs in 26.2% (N = 11) of studied patients. According to ENDA/EAACI and its position paper the most cases of NSAIDs hypersensitivity in children up to 10 years old is thought to be nonimmunological response and what is more these reactions are often triggered by the infection itself or exercise [9]. In older children the mechanisms are the same as in adults and can involve immunological and non-immunological pathways. That is why it is important to perform drug provocation tests and especially in young children a sequent DPT test with alternative drug for use in case of fever in infection is needed.

### Local and general anesthetics

Local anesthetics have been largely used in general practice of dentistry and minor surgery since many years. Reports of side effects and allergies to LAs have been available in the medical literature for many years. However, it is generally believed that IgE-dependant allergy to LAs is occasional [51–57].

The LAs are composed of a lipophilic aromatic ring which is linked to a hydrophilic amino group and are classified as esters or amides based on the linking chain [52,53]. They may lead to allergic reactions in mechanism I (immediate up to 6 h, rarely up to 24 h after anaesthesia) and IV according to Gell and Coombs [2], mediated by lymphocytes T. Clinical symptoms of type I reactions include urticaria, angioedema, bronchospasm, rhinitis and conjunctivitis, gastrointestinal symptoms and anaphylactic reactions up to and including shock. The most common clinical symptom of a late reaction (type IV) is eczema. More often adverse reactions occur in the group of esters. It is believed that para-aminobenzoic acid (PABA) – a metabolite of esters – is responsible for the allergenic effect. Due to the similarity of the structure of methylparaben and propylparaben, preservatives used to stabilize both esters and amides, it is believed that some adverse reactions are not caused by the drug itself, but by a preserva-

tive for the drug (structure similar to PABA). Amide LAs are believed to be safer, which is why they are most commonly used. In the patients suspected for allergy to LAs, investigated in this study, after performing all diagnostic procedures allergy was proved just in 2 patients. This is consist with the results of a Bhole et al. [51] review on IgE-dependant reactions to LAs. Based on the results of C studies, the incidence of IgE-mediated allergy based on LA averaged 0.97%. [51]. A recent review of Jijang et al. [57] sustained the fact allergic IgE-dependant reactions and anaphylaxis are rare and usually reported in case reports for less than 1% of adverse LA reactions. Most reactions to LAs are believed to be non-allergic or due to hypersensitivity to other agents such as preservatives, excipients and the like [15].

The main limitation of the study is the fact the authors focused on IgE-mediated allergy only. The authors are aware of the problem of non-IgE drug allergy, however, diagnostic tools for these conditions are not widely available or validated.

### CONCLUSIONS

Drug allergy is a difficult problem in the practice of a doctor and is difficult to diagnose, especially in the pediatric population. It seems that too often isolated symptoms reported during infection or disease are treated as a symptom of drug allergy, and not as a symptom resulting from the course of the disease. Further research and refinement of diagnostic techniques are needed.

#### Author contributions

**Research concept:** Daniela Podlecka

**Research methodology:** Daniela Podlecka, Agnieszka Brzozowska

**Collecting material:** Daniela Podlecka

**Statistical analysis:** Joanna Jerzyńska, Agnieszka Brzozowska

**Interpretation of results:** Joanna Jerzyńska

**References:** Daniela Podlecka, Agnieszka Brzozowska

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