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Peculiarities of drug allergy in children

SUMMARY OF DOCTORAL DISSERTATION

Medicine and Health sciences,
Medicine (M 001)

VILNIUS 2021

This dissertation was written between 2014 and 2020 at Vilnius University.

Academic supervisor:

Prof. Dr. Odilija Rudzevičienė (Vilnius University, Medicine and health sciences, Medicine – M 001).

This doctoral dissertation will be defended in a public meeting of the Dissertation Defence Panel:

Chairman – **Prof. Habil. Dr. Vytautas Usonis** (Vilnius University, Medicine and health sciences, Medicine – M 001).
Members:
Prof. Dr. Annick Barbaud (Sorbonne University, Medicine and health sciences, Medicine – M 001).
Prof. Habil. Dr. Rūta Dubakienė (Vilnius University, Medicine and health sciences, Medicine – M 001).
Prof. Dr. Regina Ėmužytė (Vilnius University, Medicine and health sciences, Medicine – M 001).
Assoc. Prof. Dr. Jūratė Staikūnienė (Lithuanian University of Health Sciences, Medicine and health sciences, Medicine – M 001).

The dissertation will be defended at a public meeting of the Dissertation Defence Panel at 2 p.m. on April 20 2021, in Auditorium Magnum of Children‘s Hospital, Affiliate of Vilnius University Hospital Santaros Klinikos.
Address: Santariškių str. 7, LT-08406 Vilnius, Lithuania
Tel. +37069778378; e-mail: neringa.stirbiene@santa.lt

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VILNIAUS UNIVERSITETAS

Neringa
STIRBIENĖ

Vaikų medikamentinės alergijos ypatumai

DAKTARO DISERTACIJOS SANTRAUKA

Medicinos ir sveikatos mokslai,
Medicina (M 001)

VILNIUS 2021

Disertacija rengta 2014–2020 metais Vilniaus universitete.

Mokslinė vadovė:
prof. dr. Odilija Rudzevičienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Gynimo taryba:
Pirmininkas – **prof. habil. dr. Vytautas Usonis** (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
Nariai:
prof. dr. Annick Barbaud (Sorbonos universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
prof. habil. dr. Rūta Dubakienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
prof. dr. Regina Ėmužytė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
doc. dr. Jūratė Staikūnienė (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Disertacija ginama viešame Gynimo tarybos posėdyje 2021 m. balandžio mėn. 20 d. 14 val. Vilniaus universiteto ligoninės Santaros klinikų Vaikų ligoninės Didžiojoje auditorijoje.
Adresas: Santariškių g. 7, LT-08406 Vilnius, Lietuva.
Tel. +37069778378; el. paštas neringa.stirbiene@santa.lt

Disertaciją galima peržiūrėti Vilniaus universiteto bibliotekos ir VU interneto svetainėje adresu:
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ABBREVIATIONS

DPT – drug provocation test
IgE – immunoglobulin E
LA – local anesthetics
NSAID – non-steroidal anti-inflammatory drug
SPT – skin prick test

SUMMARY

1. INTRODUCTION

1.1 Problem and Relevance of Drug Allergy

Drugs used to treat various diseases and conditions may cause adverse reactions in addition to their therapeutic effects. The World Health Organisation (WHO) recommends that adverse drug reactions be classified into 6 types: Type A (Augmented) type reactions are predictable, dependent on the dose, and develop from overdose or pharmacological effect of the drug; Type B (Bizzare) reactions are unpredictable, do not depend on the dose, occur while taking the usual doses meant for treatment, and may be life-threatening; Type C (Chronic) type reactions are related to long-term use of the drug; Type D (Delayed) type reactions develop some time after discontinuation of the drug; Type E (End of use) type reactions develop due to discontinuation of the drug; Type F (Failure) type reactions are considered to be unsuccessful treatment [1]. Drug hypersensitivity reactions are classified as type B reactions and are described as adverse reactions to the drug or its metabolite that are clinically reminiscent of allergies. Only those reactions the immunological mechanism of action (due to drug-specific antibodies or T lymphocytes) of which has been proven are defined as drug allergies. Until an allergy to the drug is proven, it is recommended to use the term "drug hypersensitivity reaction" [2].

To date, there is a lack of data on drug allergy in children. In children, as in adults, most epidemiological studies examine type A and type B adverse drug reactions. Most studies are predominated by type A reactions, therefore, it is difficult to estimate the true prevalence of drug hypersensitivity reactions. There is a lack of epidemiological data on the incidence of drug hypersensitivity reactions in children. In order to assess prevalence, studies are often conducted by interviewing parents/caregivers of children. The

reported prevalence of drug hypersensitivity reactions in children is believed to be lower than in adults. Most studies examining reported drug hypersensitivity reactions in most cases only assess the medical history and clinical occurrence of reported drug hypersensitivity reactions without assessing the mechanism of development. Thus, population-based and patient-reported drug allergy studies overestimate the frequency of hypersensitivity reactions and drug allergies. In clinical practice, most patients who have experienced a specific reaction associated with drug use are identified as allergic to the drug without conducting any further testing [3]. After a complete allergological examination, drug allergy is confirmed in only a small proportion of children, on average about 10% [4]. There are no unified protocols for drug hypersensitivity reactions in paediatric patients. Due to the physiological and psychological characteristics of children, it is more difficult to perform drug tests on children than on adults, and the diagnosis of suspected drug allergy often remains unconfirmed until adulthood and even throughout the patient's whole life. All of this leads to hyperdiagnosis of drug allergies and drug hypersensitivity reactions. Therefore, alternative drugs are prescribed that may be less effective, more expensive, more toxic, resulting in increased morbidity, mortality, and treatment costs [5,6].

Drug hypersensitivity reactions in children are usually accompanied by skin symptoms, the most common of which are maculopapular exanthema and delayed urticaria [4]. But these symptoms in children are often associated with viral infections. In the absence of an allergological investigation, a misdiagnosis of a drug allergy may occur, and the drug may be unjustifiably avoided, or, conversely, if these symptoms are associated only with a viral infection, in the case of a drug allergy, further use of the drug may cause allergic reactions and even life-threatening effects.

1.2 Scientific Novelty of the Dissertation

The topic of drug allergy in children has not been studied in more detail in Lithuania up until now. According to the literature, only an anonymous survey of parents in paediatric institutions was conducted. Surveyed parents reported drug hypersensitivity reactions in 7.9% of children [7], however, the proportion of children, whose drug allergy is confirmed and who are diagnosed with drug hypersensitivity reactions, has not yet been studied. Our study is the first study conducted in Lithuania that examined the frequency of confirmed drug allergies as well as clinical and diagnostic features in children. It should be noted that during the study, children were tested for drug allergies according to child-adapted protocols. Until now, the knowledge of Lithuanian primary care physicians about drug allergy in children has not been studied. This is one of the first studies in allergology and paediatrics that examined the role of primary care physicians in diagnosing drug allergy in children. In addition, there are not many studies examining patients' satisfaction with drug allergy testing, and no such study, which would assess the satisfaction of parents of children tested for drug allergy. The uniqueness of this dissertation is that drug allergy was examined in a comprehensive manner and the characteristics of paediatric drug allergies has been assessed, ranging from primary care, where assessments were made in regards to the specifics of children's drug hypersensitivity reactions and confirmed drug allergies, to the opinion of patients' parents about the benefits of drug allergy testing.

1.3 Aim of the Dissertation

To identify the peculia of suspected and confirmed drug allergy in children.

1.4 Objectives of the Dissertation

1. To assess knowledge of drug allergy in primary care and tactics chosen in counselling a child who has experienced a drug hypersensitivity reaction.
2. To determine the frequency of drug allergy among the reported drug hypersensitivity reactions and the drugs most commonly cause allergies.
3. To assess whether the medical history and clinical symptoms suggest that a drug allergy will be confirmed.
4. To assess the clinical characteristics of drug hypersensitivity reactions when drug allergy has been confirmed.
5. To assess the safety of direct provocation tests with beta-lactam antibiotics when skin tests are not performed when examining for mild delayed drug hypersensitivity reactions.
6. To assess the use of drugs after an allergological examination where the drug allergy has not been confirmed.
7. To assess the opinion of patients or their parents/caregivers on the allergological examination for drug allergy.

1.5 Theoretical and Applied Significance of the Dissertation

The data obtained in this dissertation provide information on the prevalence of drug hypersensitivity reactions in children and the importance of allergological examination. Knowledge of the peculiarities of these reactions in children may be helpful in accurately suspecting and diagnosing them. Confirmed or ruled out drug allergy during an allergological examination may help to avoid errors in prescribing drugs in the future. When drug allergy is ruled out after a previous drug hypersensitivity reaction, further avoidance of the drug is not required. There is no need to select and use alternative drugs, which are often more expensive, more toxic or less effective, and in the case of beta-lactam antibiotics, when alternative antibiotics are not

required, an increase in bacterial resistance is not expected. When a drug allergy is confirmed, a safe alternative drug is selected for the patient, thereby avoiding possible allergic reactions and future health or even life risks.

In order to reduce the hyperdiagnosis of drug allergies, it is important to educate primary care physicians and other health care professionals. The study revealed deficiencies in knowledge and choice of tactics for drug hypersensitivity reactions that could be reduced by educating physicians about drug allergies.

The assessment of the use of drugs for which no allergy has been confirmed during the allergological examination and the opinion of patients and/or their parents/caregivers about the allergological examination provides feedback and helps to assess the deficiencies and benefits of the examination from the side of the patients. All these data allow to reveal which stage of examination is to be improved, to assess whether patients and/or their parents/caregivers understand the results of allergic tests, their significance, and whether they are not afraid to use drugs for which drug allergy has not been confirmed.

A study protocol for drug hypersensitivity reactions in paediatric patients has been developed and validated in a paediatric hospital on the basis of EAACI/ENDA recommendations and recent literature data. According to this protocol, the investigation of children with drug allergies has been started in Lithuania. The data of this study create conditions for further research on drug allergy among children in Lithuania and the establishment of a drug allergy register and allow comparison with data on drug allergy in adults. The findings add to the knowledge about the prevalence of drug allergies in children in Europe.

The direct benefit to those who participated in our study was a drug allergy test and, if the drug allergy is confirmed, a safe alternative drug was selected.

1.6 Defensive Statements of the Dissertation

1. Not all children with drug hypersensitivity reactions are referred for an allergological investigation for drug allergy.
2. Most drug hypersensitivity reactions in children are manifested by skin symptoms that are not specific to drug allergy alone.
3. Drug allergy is confirmed only in a small proportion of children who have experienced drug hypersensitivity reactions.
4. There is no clinical difference between drug hypersensitivity reactions in the absence of drug allergy and reactions in which drug allergies have been confirmed following an allergological examination.
5. Direct provocation oral tests with beta-lactam antibiotics are safe in children after mild, delayed drug hypersensitivity reactions.
6. In some children, prescription and administration of the drug is avoided, even if the drug allergy is not confirmed after an allergological examination.
7. Patients' parents are positive about the allergological examination for drug allergies.

2. MATERIALS AND METHODS OF THE STUDY

During the study, a survey of outpatient health care specialists (family doctors and paediatricians) providing primary health care services to children was conducted in various Lithuanian cities. A questionnaire on drug allergy was completed by a total of 195 physicians working in primary health care. The study included family doctors and paediatricians who work in primary health care and provide services to children. Doctors with only adult patients (18 years of age and older) were excluded from the study. Doctors were interviewed from December 2015 to December 2016. Data was collected from questionnaires completed by doctors themselves, which were presented in paper or electronic form. The questionnaire was completed in only one of these ways. On average, respondents

had 488 ± 337 (2 – 1,000) children in their areas. A total of 95,116 children were in the areas of the respondents.

Children with suspected drug allergy have been investigated at Children's Hospital of Vilnius University Hospital Santaros Klinikos from December 8, 2015 to March 1, 2020. The biomedical study was performed after receiving the permission of the Vilnius Regional Biomedical Research Ethics Committee of December 8, 2015 No. 158200-15-823-334.

The subjects were selected from patients who were referred to the Children's Hospital for consultation by an allergist and who agreed to participate in this study. Children, on the basis of the medical history and clinical symptoms as well as former drug hypersensitivity reaction, were subjected to allergological work-up in accordance with EAACI/ENDA [2,4,8,9] guidelines and the drug allergy diagnostic protocol approved by the Children's Hospital (approved by Order of the Director of the Children's Hospital, PE VUH SK of October 1, 2014 No. V-228, updated by Order of April 5, 2019 No. V-119): skin tests (skin prick, skin patch, intradermal), drug provocation tests, laboratory tests (total IgE (immunoglobulin E), specific IgE, etc.). Subjects were included in the study based on defined inclusion and exclusion criteria.

Criteria for inclusion of subjects:

Patients aged 0-18 years with suspected drug hypersensitivity reactions and for whom an allergological examination for drug hypersensitivity reactions is performed at the Children's Hopistal.

Criteria for exclusion of subjects:

1. Vulnerable persons (mentally disabled, pregnant women).
2. One of the parents cannot be reached in order to obtain an informed consent.
3. Refusal to participate in the study.

A total of 91 children (45 boys and 46 girls) were included in the study. The mean age of the children at the time of the study was 8.0 ± 5.0 years. Information on children's drug allergy was collected

from their medical records (outpatient cards, inpatient and/or day care facility medical histories). The researcher completed the ENDA questionnaire and documented the results of the allergological examination for drug allergies.

After more than 1 year after an allergological examination, the patients' parents were interviewed by telephone or in person. The questionnaire is based on a questionnaire used in a clinical trial in Portugal, France and Lithuania [10], supplemented by original questions. Parents of a total of 61 patients (28 girls and 33 boys) agreed to answer the questions. The period of time that passed after the allergological examination ranged from 12 months to 5 years (mean 32.5 ± 10.4 months), and the period of time that passed from the last drug hypersensitivity reaction ranged from 16 months to 15 years (median 39 months).

Methods of Statistical analysis

The data obtained during the study were compiled into Microsoft Excel program, the purified and organised data were imported into SPSS (Statistical Package for the Social Sciences) Statistics 20 program, which was used for data analysis. Descriptive statistics were used to systematize the results of the study: arithmetic mean (M), standard deviation (SD), minimum (min.) and maximum (max.) values of results, medians, quartiles, frequencies and percentages were calculated to evaluate categorical data. The chi-square (x^2) and exact criteria were used to determine statistically significant differences between groups. In regards to the interval variables, the Mann-Whitney criterion was used to determine the differences between the two groups, and the Kruskal-Wallis criterion was used to determine the differences between more than two groups. Results were considered statistically significant when $p < 0.05$.

3. RESULTS

3.1 Knowledge of Drug Allergies in Children in the Primary Health Care Setting

Incidence of suspected drug allergy in children according to a survey of primary care physicians

The majority of primary care physicians (145 (74.4%)) indicated that there are children in their district who are suspected of having drug allergies. They were asked how many of such children are in their district. After summing up the results, it turned out that there are a total of 1,574 children suspected of drug allergy in the respondents' districts, the average number of such children in one physician's district is 16.6%.

Primary care physicians reported that they most often suspect antibiotic allergy in children (95.2%, 138 of 145). Beta-lactam antibiotics were the most commonly reported antibiotics. Penicillin and amoxicillin have been reported 91 times as drugs that might have caused allergic reactions. Among other antibiotics, cephalosporins were reported 9 times, clarithromycin – 6 times, erythromycin – 2 times, macrolides and doxycycline – each were reported once. The second leading cause of suspected drug allergy reported by physicians was NSAIDs (non-steroidal anti-inflammatory drugs) (reported by 47 (32.4%) of 145 physicians). Of the NSAIDs, ibuprofen was the most commonly reported drug in the questionnaire (17 times). Other drugs have been reported less frequently as causes of suspected drug allergy (Fig. 1). It was possible to enter own answer to the question about the suspected drugs in the questionnaire. Therefore, the "other" column listed various drugs and medical devices: ambroxol chloride, plasters, sterile bandages, herbal preparations, B vitamins, flavour enhancers in children's syrups, inhaled salbutamol were also mentioned.

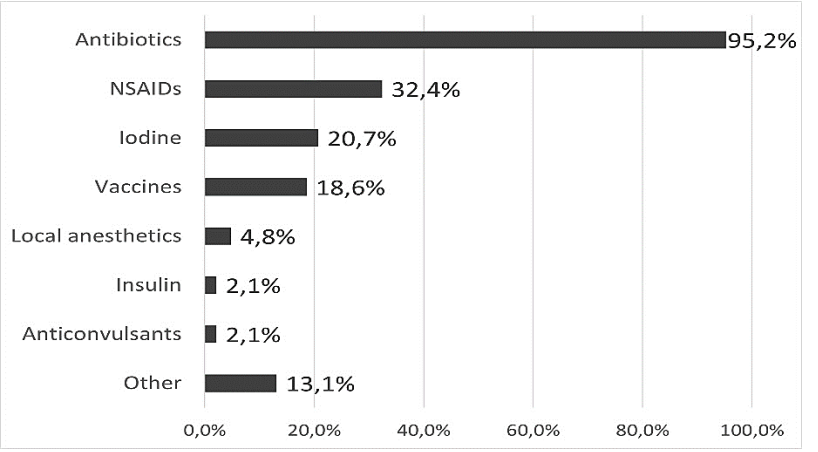

Figure 1. Suspected drugs that have caused hypersensitivity reactions in children as identified by primary care physicians.

Clinical manifestations of suspected drug allergy in children according to primary care physicians

Primary care physicians were asked about suspected drug allergy clinical symptoms. Skin symptoms were the most frequently reported symptoms in suspected drug allergy. All primary care doctors reported skin rash, 119 (82.1%) reported itchiness and 66 (45.5%) reported angioedema. Respiratory and eye symptoms were reported less frequently while cardiovascular and gastrointestinal symptoms were rarely mentioned. The clinical manifestation of suspected drug allergy in children, indicated by physicians, is summarized in Table 1.

Table 1: Clinical symptoms of suspected drug allergy in children as indicated by primary care physicians.

Symptoms	**Frequency of primary care physicians who reported suspected drug allergy in their district** (n=145)
Skin rash	100.0%
Pruritus	82.1%
Angioedema	45.5%
Eye redness, itching, lacrimation	22.8%
Sneezing, rhinorrhoea, nasal congestion	16.5%
Dyspnoea	14.5%
Diarrhoea	11.0%
Nausea	6.9%
Vomiting	6.2%
Wheezing	4.8%
Headache	3.5%
Tachycardia	2.8%
Hypotension	2.1%
Fever	2.1%
Loss of consciousness	0.0%
Other	1.4%

Tactics of primary care physicians when drug allergy is suspected in a child

We asked our respondents what tactics are used when drug allergy is suspected to evaluate clinical practice. The majority of physicians (93.8%, 136 out of 145) indicated that they discontinue the suspected drug, 99 (68.3%) physicians prescribe an alternative drug of another chemical group, and 10 (6.9%) respondents indicated that they continued treatment with the same drug with the addition of

antihistamines, and 5 (3.5%) prescribe a drug of the same chemical group.

Less than a half of respondents (41.4%, 60 out of 145) reported that they referred children with suspected drug allergy to allergist and clinical immunologist for further allergy workup.

Primary care physicians' knowledge concerning drug allergy diagnostics

The majority (69.2%, 135 out of 195) of primary care physicians were aware of the possibility to test children for possible drug allergy in Lithuania, and only 7 (3.6%) respondents indicated that children are not examined for drug allergy.

The fact that skin tests, blood test and provocation tests could be used in a drug allergy workup were indicated by 43.6% (85 out of 195) primary care physicians. Other respondents indicated not all, but only one or two of these diagnostic methods.

3.2 Peculiarities of Drug Allergy in Children

Characteristics of hypersensitivity reactions to the indicated drugs

A total of 91 children were investigated for drug hypersensitivity reactions. A total of 129 drug hypersensitivity reactions were reported in children. The majority of children (64 (70.3%)) experienced one drug hypersensitivity reaction, less frequently – two or three, and one child experienced four drug hypersensitivity reactions. Drug allergy was confirmed in 12 children who experienced a total of 27 drug hypersensitivity reactions.

The median time between the drug administration and the onset of symptoms of a hypersensitivity reaction is 5 hours. Half (53.5%) of the drug hypersensitivity reactions reported in the medical history were non-immediate. Drug hypersensitivity reactions are described in detail in Table 2.

Table 2. Characteristics of hypersensitivity reactions to the indicated drugs.

Characteristic	**Frequency**
Time after the last drug hypersensitivity reaction before allergological examination	1 month – 10 years Mean 16.8 ± 25.0 months Median 5 months
Time interval between drug administration and the onset of a hypersensitivity reaction	0 minutes – 20 days Mean 43.2 ± 61.7 hours Median 5 hours
Immediate hypersensitivity (up to 2 hours after drug administration) Non-immediate hypersensitivity (more than 2 hours after drug administration) There are insufficient data from the medical history to assess the type of hypersensitivity reaction	48 (37.2%) 69 (53.5%) 12 (9.3%)
Confirmed drug allergy: Yes No	 27 (20.9%) 102 (79.1%)

The majority of reported drug hypersensitivity reactions were caused by antibiotics (85 (65.9%) reactions), NSAIDs (23 (17.8%) reactions), and LA (local anesthetics) (16 (12.4%) reactions) (Figure 2). When the hypersensitivity reaction was caused by antibiotics, the most common cause was penicillins (64 reactions (49.6% of all drug reactions) (Figure 3)).

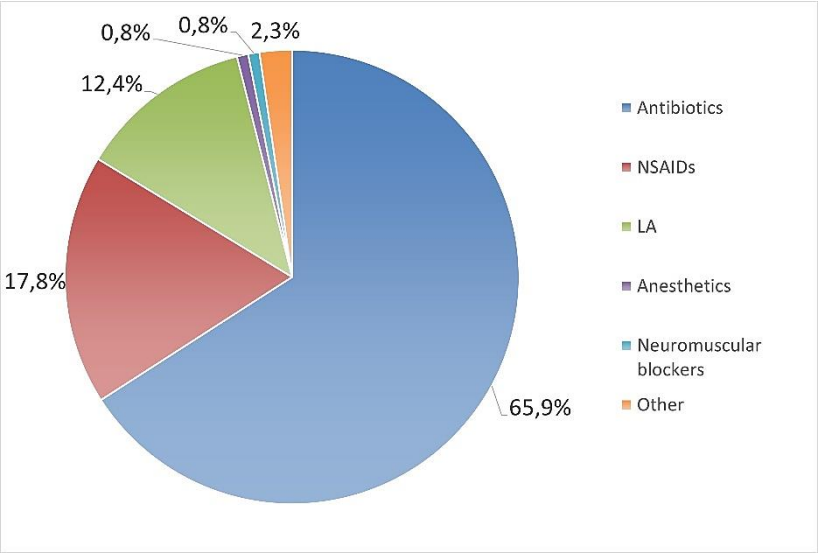

Figure 2. Drugs that have been reported to cause the hypersensitivity reactions in the children.

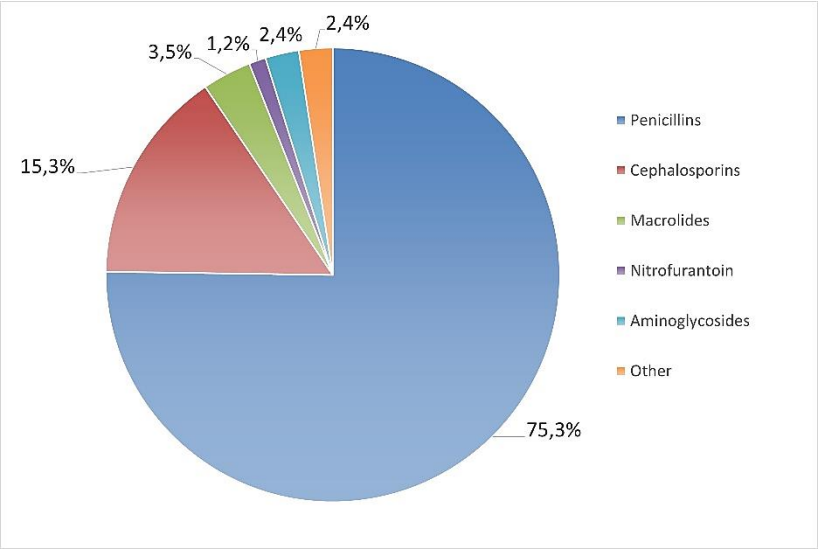

Figure 3. Antibiotics that have been reported to cause hypersensitivity reactions in the children.

The onset of symptoms of drug hypersensitivity reactions in the organ systems caused by the indicated drugs is shown in Figure 4. The reported drug hypersensitivity reactions were most commonly manifested by skin symptoms (120 (93.0%) reactions). The most following were reported to be most common: urticaria (34.9% of reactions), angioedema (33.3% of reactions), and maculopapular rash (26.4% of reactions).

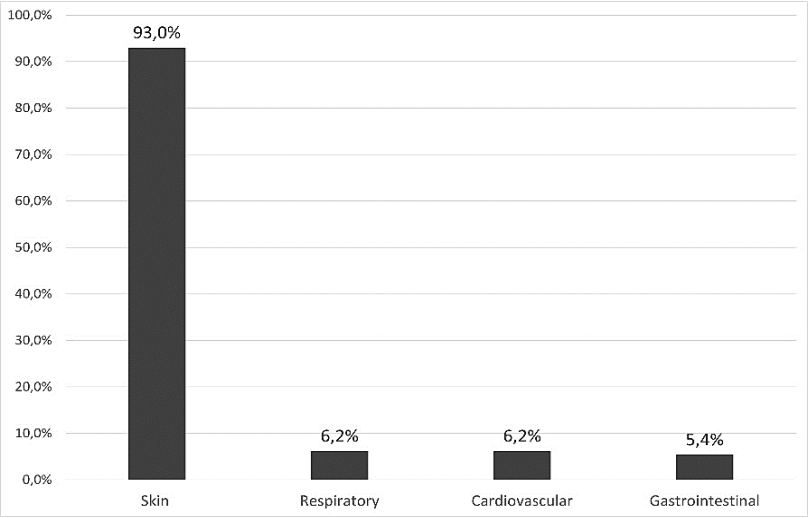

Figure 4. Symptoms of hypersensitivity reactions to the indicated drugs in the children.

Treatment of hypersensitivity reactions to the indicated drugs

The parents/caregivers of patients were asked how the drug hypersensitivity reaction was treated. The most common (80 (62.0%) reactions) treatment was with antihistamines and discontinuation of the suspected drug (67 (51.9%) reactions). One-third of the reactions were treated with corticosteroids. The use of other drugs (bronchodilators, adrenaline) to treat drug hypersensitivity reactions was significantly less common. A part of reactions (15 (11.6%) reactions) were untreated.

Peculiarities of drug hypersensitivity reactions when allergy to the medications have been confirmed in an allergological examination

When drug hypersensitivity reactions were studied in older children, drug allergy was confirmed statistically significantly more frequently ($p < 0.001$). The mean age of children with confirmed drug allergy at the time of the examinantion was 11.1 years, the median age – 14 years, and the mean age of childen with unconfirmed drug allergy at the time of the examination was 7.2 years, with a median age of 6 years. There is no statistically significant difference between the frequency of drug allergy confirmation in terms of time period after allergological examination. The type of reaction (immediate or non-immediate) did not affect the confirmation of drug allergy.

When gastrointestinal symptoms occurred during drug hypersensitivity reactions, drug allergy was confirmed statistically significantly more frequently during the allergological examination ($p = 0.035$). The occurrence of skin, respiratory and cardiovascular symptoms did not have a significant effect on the confirmation of drug allergy. In a separate examination of skin symptoms, a higher incidence of drug hypersensitivity reactions with macular rash ($p = 0.034$) was observed in children with unconfirmed drug allergy at the time of examination. When drug hypersensitivity reactions were associated with angioedema, drug allergy was confirmed more frequently ($p = 0.022$). The occurrence of maculopapular rash and urticaria did not affect the confirmation of drug allergy.

Concomitant factors and viral infection considered separately during the drug hypersensitivity reaction did not affect the confirmation of drug allergy. Co-morbidities, allergic diseases, family allergic diseases and separately examined family drug allergy also did not affect the confirmation of drug allergy.

An attempt has been made to develop a model to identify risk factors for drug allergy in children. However, there were too few confirmed drug allergy cases in our study to construct such a model.

Peculiarities of reported drug hypersensitivity reactions to beta-lactam antibiotics

A total of 77 hypersensitivity reactions to beta-lactam antibiotics (penicillins and cephalosporins) were reported in the children studied. They were experienced by 58 subjects: 30 (51.7%) girls and 28 (48.3%) boys. The mean age was 7.0 ± 5.0 years (3 months to 17 years).

The majority (42 (72.4%)) of children experienced one reaction to beta-lactam antibiotics. Penicillins caused 64 (83.1%) reactions and cephalosporins – 13 (16.9%) reactions. The most common hypersensitivity reactions from penicillins were caused by amoxicillin (44 reactions), amoxicillin with clavulanic acid (12 reactions), and penicillin (8 reactions). In the case of cephalosporins – cefuroxime (7 reactions), cefadroxil (3 reactions), cefazolin (2 reactions). There were 18 immediate reactions, 50 of non-immediate reactions, and 9 types of reactions could not be identified from the medical history.

All hypersensitivity reactions caused by beta-lactam antibiotics were associated with skin symptoms. Of these, urticaria (34 (44.2% reactions), maculopapular rash (28 (36.4%) reactions), angioedema (15 (19.5%) reactions) and macular rash (10 (13%) reactions) were the most commonly reported. Gastrointestinal symptoms occurred during 6 hypersensitivity reactions to beta-lactam antibiotics. Cardiovascular symptoms (hypotension, tachycardia) were reported in 3 (3.9%) and respiratory symptoms (cough) in 2 (2.6%) hypersensitivity reactions.

Allergy to beta-lactam antibiotics was confirmed in 5 children (8.6%). When hypersensitivity reactions to beta-lactam antibiotics were investigated in older children, drug allergy was confirmed statistically significantly more frequently ($p < 0.001$). The time elapsed after the previous reaction and the interval between the use of the beta-lactam antibiotic and the onset of the reaction did not affect the confirmation of drug allergy.

When cardiovascular ($p = 0.002$) and gastrointestinal symptoms ($p = 0.003$) occurred during hypersensitivity reactions to beta-lactam

antibiotics, drug allergy was confirmed statistically significantly more frequently. The onset of skin and respiratory symptoms did not significantly affect the confirmation of drug allergy.

Concomitant factors and viral infection examined separately during the hypersensitivity reaction to beta-lactam antibiotics did not affect the confirmation of drug allergy. Co-morbidities, allergic diseases, family allergic diseases and separately examined family drug allergy also did not affect the confirmation of allergy to beta-lactam antibiotics.

Peculiarities of reported NSAIDs hypersensitivity reactions

A total of 23 NSAIDs hypersensitivity reactions were reported in the children studied. They were experienced by 12 subjects: 7 (58.3%) girls and 5 (41.7%) boys. The mean age of subjects with NSAIDs hypersensitivity reactions was 10.8 ± 4.4 years (4 – 16 years). Co-morbidities were reported in 3 (25.0%) children: chronic sinusitis, urticaria pigmentosa and delayed urticaria were reported once. 4 (33.3%) children had allergic diseases: allergic rhinitis was reported in 3 children, while one child had food allergy.

Ibuprofen hypersensitivity reactions were reported the most times – 14 (60.9%) reactions. Hypersensitivity reactions caused by paracetamol were reported 4 (17.4%) times, citramone (acetylsalicylic acid with paracetamol and caffeine) caused 2 (8.7%) reactions, metamizole, acetylsalicylic acid and nimesulide caused 1 (4.3%) reaction each. There were 13 immediate reactions and 10 non-immediate reactions.

All NSAIDs hypersensitivity reactions were accompanied by skin symptoms, the most common of which were angioedema (17 (73.9%) reactions).

Allergy to NSAIDs was confirmed in 7 (58.3%) children who experienced a total of 16 (69.6%) NSAIDs hypersensitivity reactions. Those children studied who were confirmed to be allergic to NSAIDs were more likely to have no co-morbidities ($p = 0.020$). Confirmation

of allergy was not affected by age, time to onset after the reaction, and interval between drug administration and reaction, skin, respiratory, gastrointestinal, and cardiovascular symptoms, concomitant factors, allergic diseases of subjects, family history of allergic disease, and drug allergy in the family.

Peculiarities of reported local anesthetics hypersensitivity reactions

A total of 16 LA hypersensitivity reactions were reported in the children studied. They were experienced by 14 subjects: 5 (35.7%) girls and 9 (64.3%) boys. The mean age of subjects with LA hypersensitivity reactions was 9.8 ± 4.1 years (4 –15 years).

One subject was reported to have 3 LA hypersensitivity reactions, while one reaction was reported in regards to other children. There were 13 immediate reactions, one reaction was reported as non-immediate, and 2 reactions lacked data from the medical history in order to assess the type of reaction.

Nearly half of LA hypersensitivity reactions (7 (43.8%) reactions) were accompanied by skin symptoms, the most common of which were angioedema (6 (37.5%) reactions), macular rash was reported 3 times, and maculopapular rash was reported once. Respiratory symptoms occurred in 5 (31.3%) reactions: shortness of breath was reported 4 times (25.0%), rhinorrhea, sneezing, nasal congestion were each reported once. Cardiovascular symptoms occurred in 4 (25.0%) reactions: hypotension was reported in two (12.5%) reactions, while tachycardia and collapse each occured once. Unlike in the cases of hypersensitivity induced by other drugs, LA hypersensitivity reactions included fainting (reported 3 (18.8%) times), fear/panic and paresthesia/hyperventilation (each being reported once (6.3%)). In the case of the gastrointestinal symptoms, nausea/vomiting was reported once (6.3%). Stress was reported as an accompanying factor in 12 (70.6%) reactions.

Allergy to LA after allergological examination was not confirmed in any of the children tested.

Comparison of reported drug hypersensitivity reactions to antibiotics, NSAIDs and LA

Subjects with antibiotic hypersensitivity reactions were younger (median 6 years). Children, in regards of whom reactions to NSAIDs (median 11.5 years) and LA (median 9.5 years) have been reported, were older. The difference found is statistically significant ($p = 0.022$). Antibiotic hypersensitivity reactions were more often non-immediate, while in the case of NSAID and LA hypersensitivity, the reactioned were more often immediate ($p < 0.001$).

Skin symptoms were statistically significantly more common during antibiotics and NSAIDs hypersensitivity reactions ($p = 0.0$). Upon separate examination of skin symptoms, maculopapular rash ($p = 0.013$) and urticaria ($p = 0.001$) were statistically significantly more common in antibiotic hypersensitivity reactions and angioedema was more common in NSAID hypersensitivity reactions ($p = 0.0$). There was an increased incidence of respiratory ($p = 0.001$) and cardiovascular ($p = 0.025$) symptoms in LA hypersensitivity reactions. No significant difference in gastrointestinal symptoms was observed between the drugs.

Concomitant factors were more common during LA hypersensitivity reactions ($p = 0.001$). Reactions to different drugs did not differ significantly in the incidence of viral infection.

There were no differences between subjects who experienced hypersensitivity reactions of antibiotics, NSAIDs, and LA in terms of co-morbidities, concomitant allergic diseases, and family allergic diseases.

Peculiarities of the children when drug allergy was confirmed during the allergological examination

A total of 12 (13.2%) children were diagnosed with drug allergies: 5 boys and 7 girls. The distribution by gender did not differ significantly between children with confirmed allergy and those

without a confirmed allergy. The mean age of children with confirmed drug allergy was 12.0 ± 4.6 years and that of those without confirmed drug allergy was 7.4 ± 4.8 years. Drug allergy was confirmed statistically significantly more often ($p = 0.028$) in the school age group (7-17 years).

Allergy to antibiotics was confirmed in 5 children: in 3 children the allergy was confirmed to penicillin antibiotics and in the case of 2 children, the allergy was confirmed to cephalosporins. Allergy to NSAIDs was confirmed in 7 children: 4 children had the allergy to ibuprofen, 2 – to paracetamol, 1 – to aspirin, analgin, citramon, ibuprofen. When comparing subjects, drug allergy was more likely to be confirmed in NSAID hypersensitivity reactions ($p = 0.0$).

Children who had a confirmed drug allergy did not differ from those children who did not have a confirmed drug allergy in regards to the co-morbidities, allergic diseases, family allergic diseases.

Results of the allergy work-up of children with reported drug hypersensitivity reactions

A total of 91 children were tested for drug allergies. Drug allergy was confirmed in 12 (13.2%) children (Table 3). Skin tests confirmed drug allergy in 3 (25.0%) children. Delayed sensitization to penicillin antibiotics after a positive intradermal test with amoxicillin was confirmed in 1 subject. Immediate sensitization to cephalosporins after positive intradermal tests was confirmed in 2 children. Allergy to drugs was confirmed by drug provocation tests in 8 (66.7%) children. Sensitization to NSAIDs was approved in 4 children after positive provocation tests with ibuprofen, and sensitization to paracetamol was approved in 2 children after positive provocation tests with this drug. Sensitization to penicillin antibiotics was confirmed in 2 children after positive provocation tests with amoxicillin. In the case of one subject, sensitization to NSAIDs was confirmed by an assessment of the medical history, as the patient experienced multiple reactions to

different NSAIDs (aspirin, metamizole), and provocation tests were performed with alternative NSAIDs.

Table 3. Characteristics of subjects with confirmed drug allergy.

No	**Gender**	**Age (y)**	**Suspected drug**	**Previous reaction (s)**	**Results of allergy work-up**
1	B	8	Nimesulide Ibuprofen	Angioedema	DPT: Ibuprofen – angioedema after 1.5 hours Meloxicam – negative
2	G	7	Amoxicillin	Delayed urticaria	DPT: Amoxicillin – urticaria on day 3 after the last dose of the drug
3	G	17	Cefuroxime	Anaphylaxis	Positive intradermal tests with cefuroxime and cefotaxime after 15 minutes DPT: Amoxicillin, cefadroxil, ceftriaxone – negative
4	B	17	Amoxicillin	Maculopapular rash	Positive intradermal test with amoxicillin after 20 hours

Continued table.

No	Gender	Age (y)	Suspected drug	Previous reaction (s)	Results of allergy work-up
					DPT: Cefuroxime – negative
5	G	14	Ibuprofen	Angioedema	DPT: Ibuprofen – angioedema after 4 hours
6	G	14	Amoxicillin	Maculopapular rash, angioedema, nausea	DPT: Amoxicillin – maculopapular rash, swelling of hands and feet, weakness, nausea after 5 hours
7	B	16	Citramon Aspirin Metamizole	Angioedema	DPT: Paracetamol, meloxicam – negative
8	G	4	Paracetamol	Maculopapular rash	DPT: Paracetamol – maculopapular rash after 4 hours
9	G	11	Paracetamol	Urticaria	DPT: Paracetamol – urticaria, angioedema pruritus 10 minutes after the third dose
10	G	15	Ibuprofen	Urticaria, angioedema	DPT: Ibuprofen – itchy eyes,

Continued table.

No	Gender	Age (y)	Suspected drug	Previous reaction (s)	Results of allergy work-up
					redness, angioedema of the eyelids after 1.5 hours Meloxicam – negative.
11	B	6	Ibuprofen	Angioedema	DPT: Ibuprofen – angioedema of the lips and genitals after 1.5 hours Meloxicam – negative
12	B	15	Cefazolin	Urticaria	Positive intradermal test with cefazolin after 15 minutes

B – boy, G – girl, DPT – drug provocation test.

Peculiarities of allergological examination for drug allergy

SPTs (skin prick test) was performed in 28 (30.8 %) children. A total of 99 SPTs with drugs were performed, and all of them were negative. Most SPTs were performed with penicillin antibiotics and cephalosporins (Figure 5). Intradermal tests were performed on 27 (29.7 %) children. A total of 98 intradermal tests with drugs were performed. The drugs were the same as during SPTs, except for omeprazole, with which only SPT was performed. Of the administered intradermal tests, 4 (4.1 %) were positive: 1 with amoxicillin, 1 with cefuroxime, 1 with cefazolin, and 1 with cefotaxime. In the case of a positive intradermal test with amoxicillin, the reaction was delayed

(became positive 20 hours after the intradermal test) and in the case with other drugs, the reaction was immediate (became positive 15 minutes after the intradermal test).

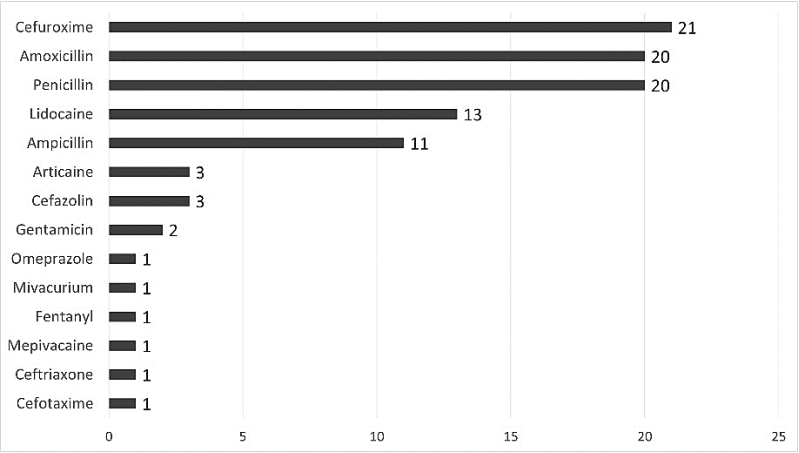

Figure 5. Drugs with which skin prick tests were performed on the subjects.

Drug provocation tests (DPTs) were performed on 87 (95.6 %) children. A total of 101 provocation tests were performed (Figure 6). Most of provocation tests were performed with amoxicillin. A total of 29 direct (without skin tests) DPTs with amoxicillin were performed. Direct DPTs were positive in only 2 children who experienced non-immediate reactions which passed after administration of treatment. Of the DPTs performed, 8 were positive (7.9 %): 4 with ibuprofen, 2 with amoxicillin, 2 with paracetamol. Immediate reactions occurred after 3 tests with ibuprofen (all 3 children developed angioedema, pruritus after 1.5 hours) and after 1 test with paracetamol (urticaria, pruritus, angioedema developed 10 minutes after the third dose). Non-immediate reactions occured after 2 tests with amoxicillin. In the first case, after 1 prolonged DPT with amoxicillin (which continued for 3 days), delayed urticaria developed 48 hours after the last dose. In the second case, maculopapular rash, swelling of the feet and hands, vomiting, weakness developed 5 hours after the last dose of DPT.

Non-immediate reactions also occured with NSAIDs: after 1 DPT with ibuprofen (angioedema of the eyelids and lips developed 4 hours after the last dose of the drug) and after 1 DPT with paracetamol (maculopapular rash developed 4 minutes after the last dose of the drug). Reactions after DPT were not severe and the symptoms of the allergic reaction disappeared after treatment. Only one case required hospitalization in an inpatient day facility after DPT, when the patient developed a rash, experienced vomiting, and weakness.

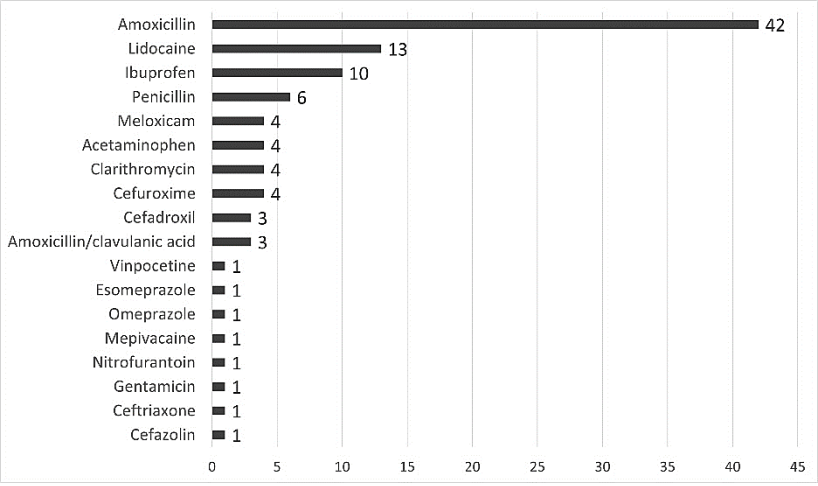

Figure 6. Drugs with which drug provocation tests were performed on the subjects.

Skin patch tests with drugs were performed on 6 (6.6 %) children. Tests with amoxicillin and penicillin were performed on 4 children, with cefuroxime – on 2 children, with cefotaxime and nitrofurantoin – on 1 child. All skin patch tests were negative.

In children examined for hypersensitivity reactions to beta-lactam antibiotics, specific IgE were performed on penicilloyl G, penicillyl V, ampicillin, amoxicillin. They were negative for all subjects (class 0).

3.3 Assessment of Drug Allergy Testing from the Perspective of Studied Childrens' Parients

Use of investigated drugs after allergological examination

The survey asked whether the child was taking the drugs after the allergological examination if the allergy to him or her had not been confirmed. The frequency of drug use was divided in practically two halves: 29 (47.5 %) children took drugs for which allergies had not been confirmed, and 32 (52.5 %) children did not use drugs. Of those who took drugs, four (13.8 % of those who took the drugs) children had adverse reactions.

When examining why patients did not use drugs after an allergological examination, most (18 (56.3 % of those who did not use drugs) children) did not need drugs in the past year. Some of the subjects continued to avoid investigated drugs (7 (21.9 %) children) or such drugs were avoided by their doctors (2 (6.3 %) children). No statistically significant difference was found between the gender of the subject, the age, the type of hypersensitivity reaction, the number of hypersensitivity reactions, the evaluation of the usefulness of the allergological examination and the evaluation score when examining whether the use of investigated drugs differs after an allergological examination depending on which drugs (antibiotics, NSAIDs or LA) have been tested for sensitization.

Benefits and deficiencies of drug allergy testing from the perspective of those studied

When asked about the deficiencies of the drug allergy testing, 47 (77.1 %) of the parents did not name the deficiencies or noted that there were no deficiencies. This question was open, so after grouping the answers of the respondents, the rest named the time spent (5 (8.2 %) children), pain, discomfort, stress during the study (4 (6.6 %) children), the fact that the drugs are given to a healthy child

as deficiencies (3 (4.9 %) children) (Figure 7). The following were mentioned as a deficiency once in each case: that fact that it was still unclear whether there was really no allergy and that the study was not conducted with the same drug that caused the hypersensitivity reaction.

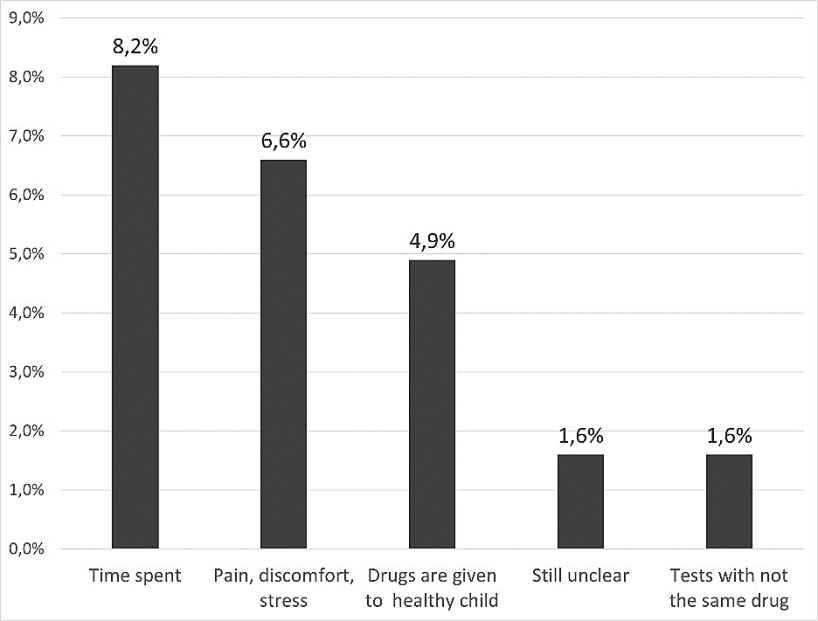

Figure 7. Deficiencies in drug allergy testing as reported by subjects who were participants in the survey on attitudes to drug allergy testing.

The survey asked to indicate the benefits of drug allergy testing. Of all respondents, 8 (13.1 %) did not state any benefits or noted that "everything was fine". After grouping the respondents' answers, the majority (27 (44.3 %)) noted that the situation became clearer to them after the examination or that the examination calmed them down (12 (19.7 %)). Some of the them distinguished the following as benefits: the medical staff involved in the study, the facilities during the study (8 (13.1 %)), others saw the fact that there were no allergic

reactions during the testing as a benefit (5 (8.2 %) children) and the fact that the result was obtained quickly (1 (1.6 %) child) (Figure 8).

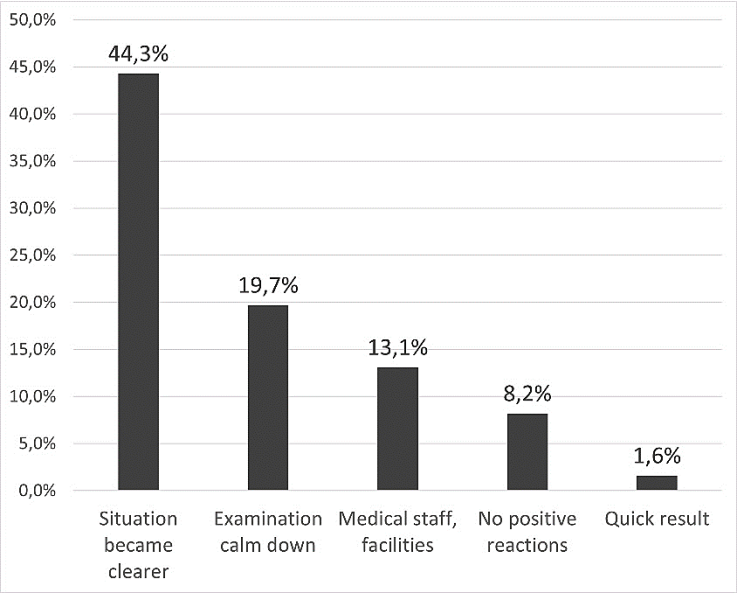

Figure 8. Benefits in drug allergy testing as reported by subjects who were participants in the survey on attitudes to drug allergy testing.

Study subjects' opinion on drug allergy testing

The majority (53 (86.9 %)) of the respondents noted that the examination on drug allergy was useful. When examining whether there is a difference in the evaluation of the usefulness of a drug allergy testing, there is no statistically significant difference between respondents who have been diagnosed with a drug allergy and those who have not. There was also no statistically significant difference in the assessment of the benefit of the testing in terms of whether or not the children used the drugs after the testing, which drugs (antibiotics, NSAIDs or LA) have been tested for sensitization from the time since the study and the last hypersensitivity reaction, the gender of the

subject, the type of previous hypersensitivity reaction, number of hypersensitivity reactions. Upon assessment by age, when an allergological examination for drug allergy was performed on school-age children (7–17 years of age), the examination was statistically significantly more often rated as useful.

All respondents indicated that the drug allergy testing was important to them. When asking to rate the allergological examination for a drug allergy on a scale from 1 to 5, when 1 is very dissatisfied and 5 is very satisfied, 52 (85.3 %) respondents gave 5 points, and 9 (14.8 %) respondents have the score of 4 (somewhat satisfied). The average score of the drug allergy testing was 4.85 points. When examining the assessment of the drug allergy testing, there was no statistically significant difference between the results of those respondents who were diagnosed with drug allergies and those who were not. There was also no statistical difference in testing scores based on whether or not children received drugs after the testing, which drugs (antibiotics, NSAIDs or LA) have been tested for sensitization from the time since the study and the last hypersensitivity reaction, the gender of the subject, age, the type of previous hypersensitivity reaction, number of hypersensitivity reactions. All respondents indicated that they would recommend an allergological examination for a drug allergy to another person with the same pathology.

4. CONCLUSIONS

1. In primary care, drug allergy is most often suspected in regards to antibiotics or when skin symptoms occur. Although most doctors know that children can be tested for drug allergies, slightly more than half of doctors refer their patients for allergological investigation.
2. Drug allergy was confirmed in 13.2 percent of children, in most cases – to non-steroidal anti-inflammatory drugs (58.34 percent of those who experienced reactions to these drugs).
3. The medical history and clinical symptoms of a drug hypersensitivity reaction are not sufficient to diagnose drug allergy.
4. Drug allergy was more frequently confirmed upon occurence of gastrointestinal symptoms, macular skin rash, angioedema and in cases where school-age children were tested.
5. Direct drug provocation tests performed without skin tests were safe in testing done on children in regards to mild non-immediate beta-lactam antibiotics hypersensitivity reactions.
6. After an allergological investigation, when allergy to the drugs has not been confirmed, almost a third of the children are still not prescribed the drugs because such drugs are avoided by their parents or doctors. The majority of children who were not confirmed to be allergic to drugs did not experience hypersensitivity reactions to the drugs investigated.
7. Parents of the children (especially older ones) rate the drug allergy testing positively and believe that an allergological investigation for drug allergy is helpful.

5. PRACTICAL RECOMMENDATIONS

1. A child who has experienced a drug hypersensitivity reaction should be referred for an allergological examination.

2. Skin and provocation tests with drugs for children should be performed according to EAACI/ENDA recommendations and tailored to the child's age, weight, and suspected drug.
3. Data on confirmed drug allergies, drugs that can cause reactions, and alternative drugs that can be prescribed should be entered in the Lithuanian e-health information system.
4. To prepare educational book for the diagnosis of drug allergy in children.
5. Based on the study data, to initiate the establishment of a drug allergy register in Lithuania.
6. To present the study data and significance of drug allergy investigation to Lithuanian physicians.

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1. Buterlevičiūtė N, Rudzevičienė O. Drug hypersensitivity reactions in children and results of diagnostic evaluation. Drug Hypersensitivity Meeting 2016. Malaga, Spain 2016
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BIOGRAPHY

Name / surname	Neringa Stirbienė
Date of birth	1986 08 19
Contact details	Santariškių str. 4, Vilnius, Lithuania Phone: +370 5 2365296 E-mail: neringa.stirbiene@santa.lt
	Education
2010-2014	Residency of Allergology and Clinical Immunology at Vilnius University
2004-2010	Medical studies at Vilnius University
	Licensure
2019-07-03	Pediatric allergist (licence No. MPL-23905)
2014-06-28	Allergist and clinical immunologist (license No. MPL-19185)
	Employment
Since 2015	„SK Impex Medical Diagnostic and Treatment Centre" as an allergist and clinical immunologist, pediatric allergist
Since 2014	Pediatrics Centre, Vilnius University Hospital Santaros klinikos as an allergist and clinical immunologist, pediatric allergist
	Training
2013	Fellowship in Academic Medical Centre of the University of Amsterdam, The Netherlands, as a winner of the EAACI Clinical Fellowship Awards 2013
2015	EAACI Allergy School „Early diagnosis and treatment of common allergic disorders in infancy and childhood", Taormina (Italy)
2016	EAACI Allergy School „Drug Allergy in Children", Belgrade (Serbia).
2017	"Specialist course in paediatric allergies", London (United Kingdom).

ACKNOWLEDGMENT

I would like to express my deepest gratitude to everyone who has helped me to write this dissertation:

To prof. dr. Odilija Rudzevičienė, the supervisor of this dissertation, who guided me and supported me in all stages of the dissertation.

To prof. dr. Regina Ėmužytė, assoc. prof. Sigita Petraitienė, assoc. prof. Anželika Chomičienė and all colleagues at Vilnius University Clinic of Children Diseases who read the manuscript and provided valuable remarks.

To all my Teachers who inspired my interest in allergy and clinical immunology, shared their experience and improved my knowledge.

To all primary care doctors who agreed to participate in the survey and all doctors who sent their patients with a suspected drug allergy for a consultation.

To the children and their parents who agreed to participate in the study: it would not have been possible to obtain any results without their participation.

To biostatistician Roma Puronaitė who helped me to analyze the majority of obtained data.

To all my family for their patience, encouragement and support to complete this work.

NOTES

Vilnius University Press
9 Saulėtekio Ave., Building III, LT-10222 Vilnius
Email: info@leidykla.vu.lt, www.leidykla.vu.lt
Print run 30