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Allergy to antibiotics in children: who is to blame and what to do?

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Allergic reactions to antibiotics are a serious issue of pediatric practice and a difficult problem for pediatricians due to difficulties of diagnostics, interpretation of anamnestic data and subsequent selection of adequate antibacterial therapy. The review describes the main types of allergic reactions to the antibacterial drugs most widely used in children. Special attention is given to drug hypersensitivity development risk factors; clinical manifestations of allergy to antibiotics and peculiarities of allergic reactions to certain drugs are described. The article dwells upon clinical approaches and algorithms of managing patients with presumed intolerance to antibacterial drugs.
Keywords: *antibiotics, antibacterial drugs, allergic reactions, drug hypersensitivity, allergy, intolerance, risk factors.*

INTRODUCTION

Antibiotics – one of the most frequently prescribed drug groups to children in outpatient practice; moreover, antibiotics cause adverse drug reactions (ADR) more frequently than any other drugs [1-3]. Despite the fact that allergic reactions to antibacterial drugs (ABD) do not have a very high percentage of all the reported ADR (ca. 25%), they are traditionally considered the most significant adverse reactions of antibacterial drug and the main cause of emergency calls in the pediatric population [3, 4]. Usually, allergic reactions are not that severe to cause hospitalization of a small patient. However, ABD allergy is a serious reason for parental concern and a complicated task for a pediatrician, as it is associated with difficulties in diagnostics and subsequent selection of an adequate antibacterial therapy [5-7]. Moreover, allergic reactions increase expenses for treatment of patients [4, 8]. Clinicians do not often resolve to prescribe antibiotics to patients with suspected, though unconfirmed IgE-mediated reactions due to a potential risk of development of life-threatening anaphylactic reactions [9].

The **aim** of this article is the review of an issue of allergic reactions to antibiotics in pediatric practice and review of clinical approaches to the management of patients with suspected intolerance to antibacterial drugs.

Terminology and pathogenetic aspects

Terms "drug allergy", "drug hypersensitivity" and "drug reactions" (adverse drug reactions) are often used in literature as interchangeable [10]. Term "adverse drug reactions" involves all adverse reactions associated with drug prescription regardless of the disease etiology, i.e. ADR are any harmful and unexpected effects due to drug use in therapeutic doses in patients for the purposes of prevention, treatment or diagnostics [11]. In 2003, the World Health Organization (WHO) defined term "drug allergy" as the immune-mediated response to a drug in a sensitized patient [12]. "Drug hypersensitivity" and "drug allergy" are synonyms, although several authors

regard term "drug allergy" applicable only to the IgE-mediated reactions [10], although the WHO does not support this concept [12].

There are 4 types of allergic reactions depending on the **mechanism of development**: immediate hypersensitivity (IH) – IgE-mediated (anaphylactic, reaginic), cytotoxic and immune complex reactions – and delayed hypersensitivity (DH) – cell-mediated reactions (tb. 1) [13].

Apart from the classic types of allergic reactions listed in tb. 1, there are rarer variants of hypersensitivity, which are difficult to classify due to the lack of proofs of prevalent nature of one of the immunological mechanisms of development, e.g., morbiliform rash in the setting of use of sulfanilamides due to the development of specific activation of T lymphocytes or Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) in the event of development of the Fas ligand-induced apoptosis [10]. The list of non-IgE-mediated allergic reactions and significant ABD are given in tb. 2.

Table 1. Types of allergic reactions [13]

Type of reaction	Description	Type of immune response	Clinical manifestations	Term of reaction development
Type I	IgE-mediated (anaphylactic, reaginic)	IgE	Urticaria, anaphylaxis, Quincke's edema, bronchospasm etc.	Minutes-hours after the exposure
Type II	Cytotoxic (cytolytic)	IgG	Hemolytic anemia, cytopenia, nephropathy etc.	Varied
Type III	Immune complex	IgG and complement	Serum-like syndrome, drug fever, vasculitis, arthralgiae etc.	1-3 weeks after the exposure
Type IV (a, b, c, d)	Cell-mediated	T lymphocytes	Contact dermatitis etc.	2-7 days after the exposure

Table 2. Non-IgE-mediated allergic reactions

Type of reaction	Causative ABD
Hemolytic anemia	Cephalosporins, chloramphenicol
Leukopenia, thrombocytopenia	Cephalosporins, co-trimoxazole, penicillins
Serum-like syndrome	β-lactams
Vasculitis	Sulfanilamides
Maculopapular exanthema	β-lactams, sulfanilamides, macrolides, fluoroquinolones
Fixed drug eruptions	Sulfanilamides, tetracyclines
Symmetrical drug-induced intertriginous exanthema	β-lactams
Acute generalized exanthematous pustulosis	Aminopenicillins, cephalosporins, sulfanilamides, fluoroquinolones
Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)	Sulfanilamides, co-trimoxazole, β-lactams
DRESS-syndrome*	Tetracyclines, co-trimoxazole

Note. * - drug-induced eosinophilia with severe systemic symptoms.

Epidemiology of allergic reactions to antibiotics in children

The real spread of allergic reactions to ABD in children is unknown. There have been far less trials dedicated to epidemiologic aspects of allergic reactions to antibiotics in pediatric practice than in adult patients, whereas the spread of hypersensitivity to antibiotics varies considerably in children, which is why it is not possible to draw a conclusion on the real frequency. According to

prospective trials, ADR frequency in children in outpatient practice is 0.75-4.5% [2, 14, 15]. There have been only few population trials determining the share of allergic reactions among the total amount of ADR. Most emergency calls due to development of ADR in the setting of antibacterial therapy in whole and of allergic reactions in particular is observed in children under 4 years of age (13.2 emergency calls per 1,000 children; 56% of all calls concern dermatological complaints, i.e. angioneurotic edema, urticaria and non-specific allergic symptoms) [3]. These data correspond with the results of the earlier trials demonstrating that allergic reactions constitute 72% of the structure of ADR to antibiotics in small children (under 4 years of age) [16]. Most publications amount to description of singular cases or a series of cases of development of allergic reactions in singular patients. Moreover, pathophysiological basis of ADR to many antibiotics is unknown, although they may be considered allergic by nature. E.g., serum sickness-like syndrome, which is developed by 0.06% of the children taking cefaclor, is most probably associated with cytotoxic effect of the drug on cells, rather than with formation of immune complexes [17, 18].
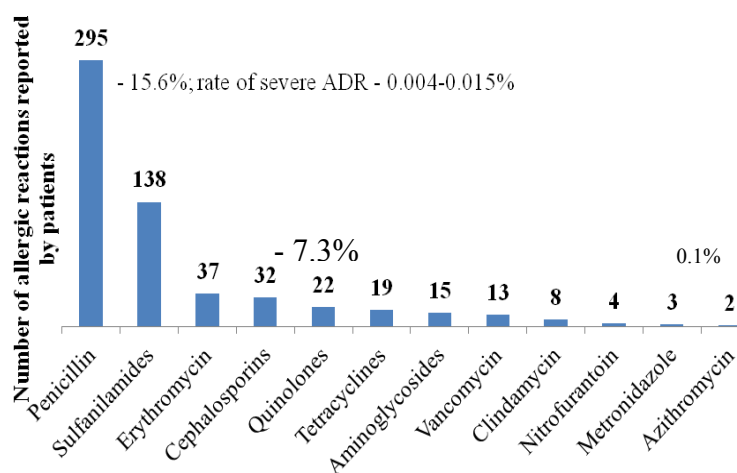
Frequency of allergic reactions to antibiotics reported by patients or patient's parents is always considerably higher than the real spread. Thus, e.g., the frequency of positive results of skin tests (i.e. confirmation of the classic IgE-mediated allergy) in patients with anamnestic data stating penicillin intolerance varies from 0 to 34% [19-23].

Among all ABD, penicillins cause allergic reactions most often; their frequency varies from 1 to 10% [24, 25]. According to a large-scale analysis performed in the framework of program Boston Collaborative Drug Surveillance Program, use of β-lactams causes skin reactions most often; their frequency is 5.1% for amoxicillin, 4.5% for ampicillin and 1.6% for penicillin [4]. Most skin reactions manifest themselves as maculopapular rash and urticaria, which is why it was difficult to determine the real share of IgE-mediated events. The frequency of life-threatening anaphylactic reactions to penicillins is far lower – 0.004-0.015% [25].

The frequency of anaphylactic reactions determined by the trial involving children and young adults who had been receiving monthly benzathine benzylpenicillin as year-round prevention of rheumatic fever for 3.4 years on the average was 1.23 per 10,000 injections; at the same time, no such cases were registered in 600 patients under 12 years of age [26].

According to a large-scale trial involving more than 1,800 patients, the highest rate of allergic reactions to ABD reported by patients was to penicillin – 15.6% (pic. 1) [27]. Azithromycin was the rarest drug to be reported by patients in anamnesis (2 cases out of 1,893 respondents, 0.1%). Similar results were obtained in the trial by C. Ponvert et al. (2011), who analyzed data of 1,431 children with anamnestic data on penicillin intolerance; the examination confirmed allergy to β-lactams in 227 (15.9%) of them [28].

Pic. 1. Rate of allergic reactions to ABD reported by the patients requiring prescription of antimicrobial therapy (n=1,893) [27]

Beyond any doubt, macrolides are the safest antibiotics in terms of development of allergic reactions: thus, frequency of emergency calls due to development of allergic reactions (both mild and severe) per 1,000 ABD prescriptions was the lowest in the group of macrolides (tb. 3) [29].

Table 3. Rate of emergency calls due to development of allergic reactions [29]

ABD	Allergic reactions	
	Mild	Moderate/severe
Penicillins	7.6	2.2
Cephalosporins	2.8	1.3
Macrolides	1.7	1.1
Lincosamides	8.4	2.8
Fluoroquinolones	2.8	2.4
Tetracyclines	2.0	1.2
Co-trimoxazole	8.3	4.3

Risk factors of development of allergic reactions to antibiotics
Risk factors of development of allergic reactions to antibiotics may be divided into 3 categories for convenience:
1) ABD risk factors;
2) risk factors associated with concurrent diseases and therapy;
3) risk factors associated with the patient [30].
ABD risk factors involve a certain antibacterial drug, its metabolic peculiarities, dosage regimens and modes of administration. Most immunologically-mediated reactions concern ABD metabolites. E.g., penicillin itself has low immunogenicity; however, it is rapidly metabolized with several resulting immunologically reactive determinants. Singular preventive doses (e.g., in surgery) of drugs prescribed on a singular basis or in short courses (e.g., azithromycin) cause sensitization far rarer than long-term intake of high doses of antibiotics or parenteral administration of ABD. Frequent repeated courses are more likely to result in the development of an allergy than therapy courses with interval of several years. In order of sensitization risk, modes of ABD administration are as follows: local > parenteral > peroral. Local administration primarily causes development of DH, parenteral – of anaphylactic reactions [30].
Risk factors associated with concurrent diseases and therapy. The frequency of allergic reactions to antibiotics increases at a range of diseases. A significantly higher frequency of maculopapular rash, e.g., in the event of use of ampicillin (50-80%) or co-trimoxazole, is observed in patients with infectious mononucleosis, cytomegalovirus infection, HIV infection and in children with oncohematological diseases (acute leucosis, lymphomas) undergoing cytostatic therapy. Children with mucoviscidosis develop bronchospasm as a manifestation of drug allergy to ABD more often than other patients [30].
Opinions on the role of atopic diseases (food allergy, bronchial asthma, pollinosis, atopic dermatitis) as a risk factor of development of allergic reactions to antibiotics are contradictory. Some experts deem it unreasonable to restrict the use of ABD on the basis of presence of atopic disease only. Most publications featuring this statement quote the trial by E. Haddi et al. (1990), who compared frequency of detection of specific IgE to air allergens in patients with anamnestic data of systemic allergic reactions to drugs. The main conclusion of that doubtful work in terms of the applied methods was that atopic disease is not a risk factor of development of systemic allergic reactions to drugs [31]. This statement has been dramatically reviewed by the "Drug allergy: an updated practice parameter" issued in 2010 by the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology), which states that atopic disease is a risk factor of development of drug hypersensitivity to drugs in whole and to ABD in particular [30]. Thus, the trial published in 2010 demonstrated that atopic disease is a significant risk factor of

development of hypersensitivity to β-lactams [32]. The odds ratio of allergic reactions to penicillins is 3.86 in patients with allergic rhinitis, 3.12 in patients with night cough and 9.9 (!) in patients with food allergy, i.e. in the latter case we encounter with an almost tenfold increase in the risk of development of hypersensitivity to β-lactams in patients with food allergy, while food allergy is the most widespread allergy in childhood [32]. Moreover, it ought to be remembered that anaphylactic reactions may take a severer course in patients with atopic disease (bronchial asthma etc.).

Some drugs may alter intensity of the drug allergy. E.g., β-blockers increase the risk of development and intensity of anaphylactic reactions and decrease efficacy of adrenaline used to terminate them. Concomitant glucocorticoid therapy may decrease intensity of allergic reactions. It ought to be remembered as well that the belief in preventive effect of antihistamine drugs used to prevent development of real (not pseudoallergic!) allergic reactions both to antibiotics and other drugs is profoundly erroneous [30, 33, 34].

Risk factors associated with the patient are age, sex, specific genetic polymorphism, constitutive peculiarities, previous allergic reactions and congenital susceptibility to reactions to several different drugs (multiple drug allergy syndrome) [30]. The children whose parents have allergy to ABD feature a 15 times higher risk of development of an allergy to antibiotics. Drug allergy is less intense and takes a milder course in smaller children and the elderly. It has been observed that women develop allergic reactions to antibiotics ca. 30% more often than men [35]. Allergy to any drug stated in the anamnesis is a risk factor of development of allergic reactions to penicillin as well. At the same time, patients with penicillin intolerance have a 10 times higher risk of development of reactions to ABD, than the population in whole. The main facts and myths concerning the allergy to β-lactams are given in tb. 4 [36].

Table 4. Facts and myths about allergy to β-lactams

Atopic diseases (atopic dermatitis, eczema, food allergy, bronchial asthma, pollinosis, allergic rhinoconjunctivitis etc.) are a risk factor of development of allergic reactions to antibiotics	True
Hypersensitivity to fungi affects development of allergic reactions	False
Smaller ABD doses are safer	False
Intravenous administration of antibiotics is a procedure of high risk	True
Earlier allergic reactions to AMD increase the risk of allergy to β-lactams	True (6-10 times)
Allergic reactions to penicillins completely rule out possibility of using cephalosporins	False

Table 5. Antibiotic-induced allergic reactions [37]

ABD groups	Possible allergic reactions
Penicillins	Urticaria, angioneurotic edema (Quincke's edema), anaphylaxis, maculopapular rash, exfoliative dermatitis, vesicular rash, multiform exudative erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum-like syndrome, vasculitis, cytopenia
Cephalosporins	Urticaria, Quincke's edema, anaphylaxis, maculopapular rash, multiform exudative erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction, aplastic anemia, hemolytic anemia
Sulfanilamides	Urticaria, Quincke's edema, anaphylaxis, maculopapular rash, exfoliative dermatitis, multiform exudative erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis, allergic myocarditis, polyarteritis nodosa, serum-like syndrome, photosensitization reactions
Macrolides	Urticaria, Quincke's edema, anaphylaxis, mild skin reactions

Clinical manifestations of the allergy to ABD
Clinical manifestations of the allergy to ABD vary considerably depending on type, severity of reactions and the affected organ. Allergic reactions to the most widely used groups of antibiotics in pediatric practice are given in tb. 5 [37].

The most frequent manifestations of allergic reactions to ABD are IgE-mediated reactions, i.e. urticaria and Quincke's edema; other variants of anaphylactic reactions appear rarer. Usually, they are developing for several days (usually – a week) after the initial drug's effect (sensitization period); reactions develop much earlier (from several minutes to several hours depending on peculiarities of the body, drug type, mode of administration and other factors) in the event the allergen affects the patient again. As far as clinical manifestations of this type of drug hypersensitivity are well known, we are not considering them in detail in this review; we draw attention to several other drug hypersensitivity manifestations, which may be frequent or rare, but certainly significant from the clinical point of view.

The phenomenon of the so called ampicillin rash cannot be ignored; it is a widespread reaction to antibiotics, which develops in patients in the setting of use of aminopenicillins (ampicillin, amoxicillin, inhibitor-protected aminopenicillins) [38-41]. Frequency of ampicillin rash development is 5-10%; it may reach 75-100% (32.9%, according to the data of 2013) in the event of the infection caused by Epstein-Barr virus (i.e. in the event of infectious mononucleosis) [30, 38-40, 42]. Its distinctive feature is maculopapular rash (described for the first time in 1960s); it is not truly allergic in terms of the mechanism of development; it is not considered a risk factor of development of life-threatening reactions to penicillin; it manifests on the 4th-5th day of aminopenicillin therapy; it is not accompanied by pruritus; it passes itself within 3-6 days and does not usually pose a contraindication to the future use of aminopenicillins. However, several guidelines state that several patients may require skin tests in order to rule out the possibility of a true IgE-mediated hypersensitivity to penicillin due to insufficiently clear anamnestic data on the development of such a reaction to ABD; in the event that testing results are positive, it is necessary to decide whether to prescribe alternative antibacterial drugs or not [30, 43, 44]. It ought to be mentioned that age, sex and atopic anamnesis are not risk factors of development of ampicillin rash.

Use of certain ABD may affect viscera. Cases of development of hemolysis and cytopenias, which were most probably caused by the antibodies specific to a certain drug, were registered in the event of use of cephalosporins or of high doses of penicillin [45].

Drug fever is an extremely interesting variant of allergic reaction to ABD. Its development is often associated with use of penicillins, cephalosporins and sulfanilamides (especially in patients with HIV infection). On the average, drug fever develops 6-8 days after the treatment has begun. Drug fever may be suspected in a patient in the event of concurrent rash and/or eosinophilia (90% of patients) or when the patient's condition does not correspond to the fever. Patients usually bear temperature rise well and do not complain of rigor or myalgia, while the temperature rises to 39-40.5°C, though it may be <39°C. The most reliable permanent symptom of drug fever is relative bradycardia (lack of correspondence of heart rate to temperature rise). Rapid pulse at temperature rise may indicate an infectious process. Thus, we may speak of 3 main (fever, eosinophilia, bradycardia) and 1 additional (body temperature normalization 48-72 hours after AMD withdrawal) diagnostic criteria [23].

Acute drug-induced interstitial nephritis may be caused by β-lactams, sulfanilamides and tetracyclines. Most often, it manifests itself without explicit symptoms; may be concurrent with exanthema in rare cases. Pain syndrome in the lower back and general weakness are the only symptoms until the development of renal failure [46].

Fever, arthralgia, macular and urticarial rash, lymphadenopathy and sometimes edema are classic clinical manifestations of **serum sickness**. Typical serum sickness that started 1-3 weeks after injection was previously caused by wide use of heterogenous serums. At present, serum-like syndromes with latent period of 6-8 hours are most often caused by protein-free drugs, mainly,

penicillins and cephalosporins. Drug-induced serum-like syndrome usually terminates by itself; total duration of symptoms does not exceed 1-2 weeks [47, 48].

The severest and most serious in terms of patients' life and health prognosis hypersensitivity reactions to antibiotics are severe skin allergic reactions (Stevens-Johnson and Lyell's syndromes) and drug-induced hypersensitivity syndrome (or drug-induced eosinophilia with systemic symptoms).

Drug-induced hypersensitivity syndrome cannot be considered a widespread manifestation of drug allergy, although severity of clinical manifestations and potentially severe consequences substantiate necessity of describing this syndrome [49, 50]. Thus, drug-induced hyperreactivity syndrome-associated mortality is ca. 10% and is primarily related to the development of hepatic failure. Term "drug-induced hypersensitivity syndrome" (DIHS) is synonymous to terms "drug reaction and eosinophilia with systemic symptoms" (DRESS) and "drug hypersensitivity syndrome" [49]. Typical manifestations and symptoms include macular (spotty) exanthema, fever, weakness, edema of lymph nodes and involvement of various organs and systems (hepatitis – 50%, nephritis – 10%; pneumonitis, colitis and pancreatitis are observed less frequently) [49-51].

DRESS is often induced by tetracyclines and is most often clinically manifested with lymphadenopathy. More than 70% of patients with DRESS observe intense eosinophilia. It ought to be mentioned that DRESS symptoms may appear within 12 weeks since the beginning of treatment, especially after increasing the drug's dosage. Hypersensitivity manifestations and symptoms may persist and recur for many weeks after the causative drug has been withdrawn. Relapse of symptoms, especially in the 3rd week, is typical. It is usually caused by reactivation of herpesvirus, especially of herpesvirus 6, Epstein-Barr virus or cytomegalovirus [52].

Diagnostic criteria for DRESS diagnosis include the following clinical and paraclinical symptoms [53]:
1) maculopapular rash >3 weeks into the treatment;
2) persistence of clinical symptoms after the causative drug has been withdrawn;
3) fever (>38°C);
4) hepatic dysfunction (ALT>100 IE/l) or involvement of other organs and systems;
5) peripheral blood disorders that may involve at least 1 of the following symptoms:
- leukocytosis (>11x10^9 cells/l);
- atypical lymphocytosis (>5%);
- eosinophilia (>1.5x10^9 cells/l);
6) lymphadenopathy;
7) herpesvirus 6 reactivations detectable 2-3 weeks after development of symptoms.

Presence of all 7 criteria confirms diagnosis "typical drug-induced hypersensitivity syndrome"; presence of 5 criteria is considered to be a symptom of atypical drug-induced hypersensitivity syndrome.

The most dangerous ADR are severe skin syndromes – multiform exudative erythema, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) [30, 54-57]. It has been established that co-trimoxazole causes the mentioned reactions more often than any other modern ABD.

These syndromes may take both an independent course and shift from mild to severe form. Multiform exudative erythema is characterized by development of polymorphic erythematous rash, often 10-14 (sometimes up to 3 weeks) since the patient has started taking an antibiotic. Rash is usually symmetrical and localized on distal areas of limbs; it is only rarely widespread; represented by multiple roundish papules (rarer - by vesicles) forming ring-shaped multicolored eruptions. The condition's severity and outcome depend on visceral lesion. Multiform exudative erythema-associated mortality is less than 1% [55-57].

Stevens-Johnson syndrome is characterized by involvement of mucous tunics (90%), conjunctiva (85%) and development of cavitary elements (vesicles, rarer – bubbles) in pathological process. Epidermal rejection at Stevens-Johnson syndrome is observed on not more than 10% of body

surface. Fever and flu-like symptoms often precede lesion of skin and mucous tunics by 1-3 days. Visceral involvement is prognostically unfavorable; mortality may reach 30% [54-57].

Toxic epidermal necrolysis (Lyell's syndrome) is a severe toxicoallergic reaction with fever, formation of bubbles, epidermal rejection on more than 30% of body surface and visceral lesion [58]. The highest mortality is observed at Lyell's syndrome (40-80%, according to different authors) [54-57].

One of the key points of treating severe forms of drug allergy is as fast as possible withdrawal of the causative drug. Further management tactics for patients with severe allergic syndromes depends on the syndrome [58]. Thus, it is advisable to prescribe systemic glucocorticoids in the dosage of 1-2 mg/kg per day within the first 72 hours of Stevens-Johnson syndrome as soon as possible, whereas prescription of systemic glucocorticoids at Lyell's syndrome is not advisable: there has been a sufficient number of cases where risk exceeded benefit (increase in frequency of infectious complications, which results in mortality increase). There is information that it is reasonable to prescribe intravenous immunoglobulin in high dosage (0.8-3 g/day) at toxic epidermal necrolysis, as it reduces general mortality down to 20% [58]. The "Drug allergy: an updated practice parameter" (USA, 2010) states that reasonability of prescribing glucocorticoids at multiform exudative erythema and Stevens-Johnson syndrome and of intravenous immunoglobulin at toxic epidermal necrolysis is disputable, although not repudiated [30]. At the same time, it is absolutely not advisable to prescribe systemic glucocorticoids at Lyell's syndrome [30]. It is advisable to prescribe systemic glucocorticoids in the dosage of 0.5-1 mg/kg per day for 6-8 weeks with gradual withdrawal in the event of drug-induced eosinophilia with systemic symptoms [58].

Peculiarities of allergic reactions to ABD groups and certain drugs
Anaphylactic reactions, including severe cases of anaphylaxis, are theoretically possible to any ABD; however, type 1 allergic reactions most often develop to **penicillin**. Penicillins and cephalosporins contain a tetramerous lactam ring – a general antigen determinant causing polyvalent allergy within these ABD groups. Benzylpenicillin is one of the most frequent causes of anaphylaxis and other immediate allergic reactions. Most patients with penicillin allergy react in the same way to polysynthetic penicillins. Reactions to aminopenicillins are peculiar due to high frequency of development (5-9%) of maculopapular (morbiliform) eruptions [59].

Allergy to **cephalosporins** most often manifests itself in the form of eosinophilia (3-8%), maculopapular eruptions (1-3%), drug fever (2%) and positive Coombs test (1-2%). Sometimes it may also manifest itself in the form of urticaria, serum-like reactions and anaphylaxis (0.0001-0.1%). In order of allergic reaction risk reduction, the drugs are as follows: ceftriaxone > cefoperazone > cefoxitin > ceftazidime > cefotaxime > cefuroxime [60]. The risk of development of cross-reactions to cephalosporins in patients with penicillin allergy is the highest (10-15%) for generation I cephalosporins and the lowest (1-2%) for generation III-IV drugs. Severe allergic reactions are rare. Hematologic reactions to cephalosporins are rather rare; there have been documented cases of eosinophilia, neutropenia, thrombocytopenia, hemolytic anemia [61].

Sulfanilamides in whole and **co-trimoxazole** in particular may be considered a sort of "leaders" among antimicrobial drugs in terms of frequency and variety of the caused ADR, which are often life-threatening (severe skin syndromes, anaphylaxis, thrombocytopenia, hemolytic anemia etc.). Co-trimoxazole is one of the most frequent causes of development of skin allergic reactions (fixed erythema, urticaria, Quincke's edema, erythema nodosum, allergic vasculitis) – in 3.5% of patients [62]. The most dangerous co-trimoxazole-associated ADR are severe skin syndromes: multiform exudative erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis. It has been established that co-trimoxazole leads to the mentioned reactions more often than any other modern ABD. Relative risk of co-trimoxazole-associated development of Stevens-Johnson syndrome or toxic epidermal necrolysis is 12 times higher than when cephalosporins are used, and 16 times higher than when fluoroquinolones are used [63]. Use of co-trimoxazole is the most

frequent cause of fixed drug eruptions with various clinical manifestations (ring-shaped hyperpigmented macules, erythema, urticaria) [64]. Drug fever, interstitial nephritis and aseptic meningitis may also develop as a manifestation of hypersensitivity to co-trimoxazole, though more rarely. According to long-term trials conducted in the Netherlands, co-trimoxazole is the number one ABD in terms of rate of development of anaphylactic reactions [65]. Patients with deficit of glucose-6-phosphate dehydrogenase often develop hemolytic anemia in the setting of co-trimoxazole intake. There have been cases of aplastic anemia, agranulocytosis and leukopenia. Registration of all cases of drug-induced thrombocytopenia in Denmark in 1968-1991 allowed establishing that co-trimoxazole causes this condition more often than any ther ABD [66, 67].

According to epidemiological trials, **macrolides** are among the safest ABD [68]. Allergic reactions to macrolides are very rare and usually manifest themselves in the form of urticaria and maculopapular exanthemas [69]. There have been singular cases of anaphylaxis as a reaction to erythromycin. There are no data on polyvalent allergy to several macrolides simultaneously.

Chloramphenicol (levomycetin) may cause allergic reactions of 2 types: anaphylactic reactions (sudden arterial pressure fall, tachycardia, skin allergic reactions, urticaria, bronchospasm, Quincke's edema etc.), which may take place even when the drug is applied locally (e.g., eye drops or ointments with chloramphenicol), and delayed hypersensitivity reactions (e.g., contact dermatitis when the drug is used in pharmaceutical forms for local application), though such ADR are rare (IH) and very rare (DH) [70-74]. There are literature data on development of Jarisch-Herxheimer reaction to chloramphenicol in patients with typhoid fever, which appeared within 24 hours of the treatment and manifested itself with fever, arterial pressure fall, edema, tachycardia, nausea, myocarditis and rash [75]. Use of chloramphenicol may result in development of severe and potentially fatal ADR, including cases of severe hematotoxic reactions (aplastic anemia, suppression of bone marrow hemostasis), although such ADR are not exactly allergic.

Diagnostics and main aspects of management tactics for patients with allergy to antibiotics
Type and clinical manifestations of the developing immune response depend on the applied drug, nature of the treated disease, the patient's immune status and several other factors. That is why it is rather complicated to determine mechanism of ADR development and, more importantly, further management tactics for the patient in many cases, as clinical anamnestic data are the primary criteria of detecting a possible true allergy to antibiotics. The key points in each case may include character of the symptoms, term of reaction development after prescription of antibiotics, persistence of symptoms (term) and concomitant intake of other drugs (including over-the-counter drugs) and bioactive supplements. Numerous trials demonstrated that only few patients complaining of allergic reactions to antibiotics really featured such hypersensitivity. Even if a patient's record form features distinct anamnestic data on IgE-mediated reactions, testing results do not always confirm persistent presence of the specific IgE; this fact hinders further application of the specific drug.

In most cases antibiotics are prescribed in order to treat the suspected or confirmed infectious disease. However, it has been clearly established that the infection itself is a potential trigger factor of development of urticaria and Quincke's edema. The infection itself may cause ca. 40% of all urticaria cases in adult patients [76, 77]. Complement system activation during an infectious disease also stimulates degranulation of mast cells [78]. In most cases antibiotics are considered the cause of eruptions or edema; however, the aforementioned undoubtedly explains the fact that a significant number of patients with distinct allergic reactions to antibiotics the latter are not confirmed by the presence of specific IgE or skin test results. It is extremely complicated to clearly differentiate between the mediated infection and the true immediate drug hypersensitivity (IgE-mediated) on the basis of clinical presentation only; time aspect does not always facilitate detection of the real cause of urticaria or Quincke's edema. Moreover, several

drugs are prescribed concomitantly or successively, which is why it may be extremely complicated to determine which of the drugs has caused the allergic reaction.

The list of applicable laboratory tests and principles of managing patients with different types of allergic reactions are given in tb. 6 [10]. Unfortunately, many laboratory tests designed to detect various types of allergic reactions cannot be done at most medical establishments of Russia.

Detection of specific IgE-antibodies in blood serum is characterized by high specificity (97-100%), but low sensitivity (29-68%), which is why positive response has high prognostic value, negative response – low prognostic value (allergy cannot be completely ruled out even if no antibodies to ABD are present) [30, 58]. The only detectable specific serum IgE-antibodies are antibodies to penicillin, its derivatives and cephalosporins. This diagnostic method is not suitable for patients who had had allergic reactions to β-lactams long before due to possibility of self-elimination of antibodies. Moreover, results of detection of specific IgE do not correspond with skin test results rather often [30, 58].

Table 6. Diagnostics and management tactics for patients with drug hypersensitivity [10, 30]

Type of reaction	Laboratory examinations	Therapeutic approach
Type I (IgE-mediated)	Skin allergy tests (scratch, prick, intracutaneous tests), detection of specific blood serum IgE (RAST*, ELISA), serum tryptase**	Immediate withdrawal of the causative drug, therapy of emergencies (assessment of the need in prescription of adrenaline, systemic glucocorticoids, antihistamine drugs, bronchodilators), hospitalization in the event of severe course of the allergic reaction
Type II (cytotoxic (cytolytic))	Direct and indirect Coombs tests	Immediate withdrawal of the causative drug, assessment of the need in prescription of systemic glucocorticoids, hemotransfusion in the event of severe course
Type III (immune complex)	ESR, C-reactive protein, detection of immune complexes, antinuclear antibodies, anti-histone antibodies, tissue biopsy for fluoroimmunoassay	Immediate withdrawal of the causative drug, assessment of the need in prescription of non-steroidal anti-inflammatory drugs, systemic glucocorticoids, plasmapheresis in the event of severe course
Type IV (delayed, cell-mediated)	Application skin test, lymphocyte proliferation assays	Immediate withdrawal of the causative drug, assessment of the need in prescription of topical or systemic glucocorticoids (in the event of severe course)

Note. * - radioallergosorbent test (RAST; semi-quantitative method of detecting blood serum IgE-antibodies); ** - tryptase, or serine proteinase, released from mast cells is the only available blood assay for diagnostics of acute allergic reactions at present; *** - only in research purposes. ESR – erythrocyte sedimentation rate, ELISA – enzyme-linked immunosorbent assay.

Prick and intracutaneous allergic tests (skin tests) are used for diagnostics of IgE-mediated reactions to penicillins, rarer – to aminopenicillins and cephalosporins [30, 79, 80]. Skin testing is the most reliable diagnostics method for type 1 allergic reactions to β-lactams (prognostic value of negative response – 100%, of positive response – 40-100%), though it is completely useless in respect to non-IgE-mediated allergic reactions (e.g., serum-like syndrome, hemolytic anemia, drug fever) [6]. Diagnosticum Diater (Diater Laboratories, Madrid, Spain) has been used in Europe since 2007, PrePen (Allerquest, LLC, USA) – in the USA since 2009. Diagnosticum PrePen contains benzylpenicilloyl polylysine (primary determinant + polylysine), Diater – primary determinant + mixture of secondary determinant (penilloat, penicilloate, penicillin, penicanyl), since it is not advisable to use skin tests without the primary determinant. It ought to be mentioned that severe reactions to tests are extremely rare [80]. Unfortunately, no skin testing

allergens for diagnostics of allergic reactions to penicillins have been registered in Russia as yet. Given high cost of this type of examination, we cannot but hope that such tests will be available to Russian patients in the nearest future. That is why in this article we do not describe in detail skin testing technique for detection of allergy to antibiotics and subsequent desensitization procedure in the event that the ABD, to which the child is allergic, is the only therapeutic variant. However, we must emphasize that use of native benzylpenicillin drug for skin tests, to which some Russian medical establishments may resort, is absolutely **inadmissible**.

Skin tests (prick test and intracutaneous test) for native cephalosporins have not been standardized; however, positive results of skin tests using non-irritating concentration of cephalosporins (tenfold dilution of the full dose of 10 mg/ml for most cephalosporins) indicate presence of specific IgE-antibodies. Negative test results do not rule out risk of an allergy. Skin tests for penicillin are recommended for patients with allergic reactions to penicillin stated in the anamnesis before cephalosporins may be prescribed [30].

Negative results of skin tests using the primary and secondary penicillin determinants in patients with anamnestic data on IgE-mediated reactions to penicillin (regardless of severity) constitute grounds for safe prescription of cephalosporins. Positive results of skin tests for penicillin indicate the need in prescribing alternative AMD (not β-lactams) or cephalosporins with challenge. In case skin testing is not possible, physicians ought to be guided by anamnestic data and objectively evaluate the need in treatment with a very specific AMD (e.g., a β-lactam) [30].

The algorithms of use of penicillins (pic. 2) and cephalosporins (pic. 3) in patients with reported penicillin allergy introduced in 2011 are rather logical and useful from the practical point of view. However, as long as no skin tests for penicillin have been registered in Russia so far and clinical anamnestic data on β-lactam intolerance are in many patients uncertain or absent, the only acceptable algorithm is the possibility of using alternative antibiotics (e.g., modern macrolides with advanced pharmacokinetic properties, i.e. azithromycin, are an optimal choice for respiratory tract infections in outpatient pediatric practice).

Pic. 2. Algorithms of use of penicillins in patients with reported penicillin allergy [81]
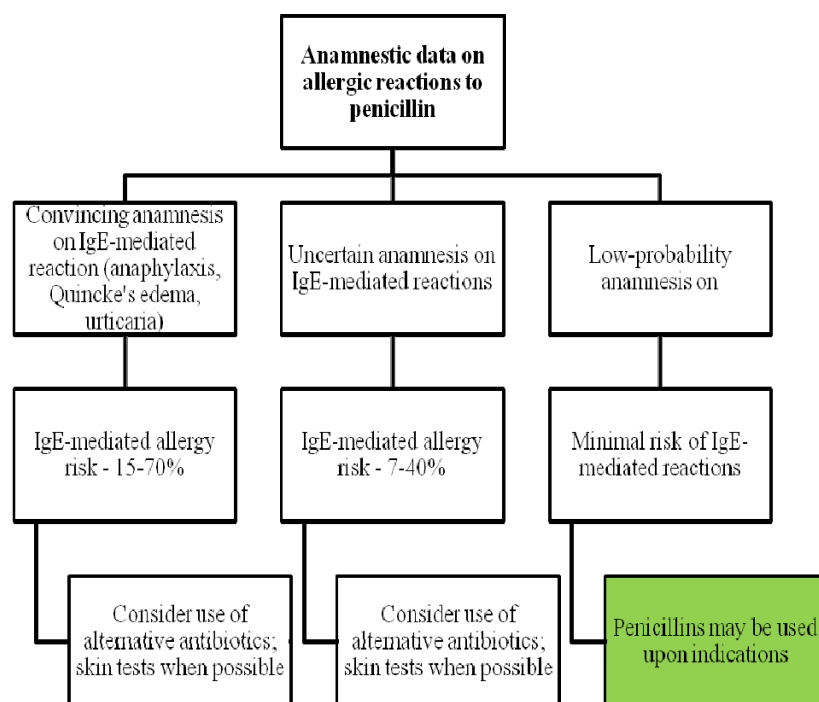
Pic. 3. Algorithms of use of cephalosporins in patients with reported penicillin allergy [81]
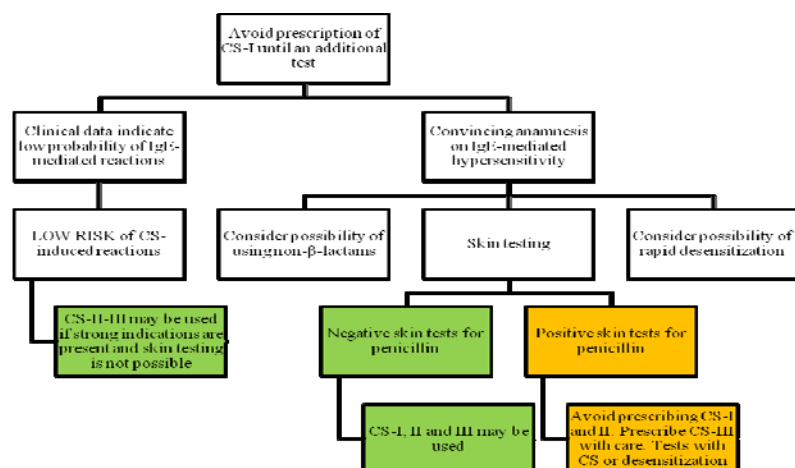
If it is impossible to replace the antibiotic, which probably is the cause of the allergic reaction, a challenge is required [30, 80, 82]. Contraindications to challenge are Stevens-Johnson or Lyell's syndrome at an earlier age. Patients and their parents must be informed on the possible risk; the challenge can only be performed if they consent to it. The procedure is to be performed by an experienced specialist prepared to render care to patients with anaphylactic reactions. Tests must be performed at medical establishments with resuscitation and intensive care units or a room equipped to provide emergency care in the event of an anaphylactic reaction. A challenge starts with 1/100 of the singular therapeutic dose. In the event of no allergic manifestations, the antibiotic is to be taken every 15 minutes (parenteral administration) or 60 minutes (ingestion) in the amount of 1/10 of the singular dose. The dose is to be 10 times higher, i.e. equal to the therapeutic dose, for the next administration in the event of a negative result. If the patient experienced severe anaphylactic reactions within the latest year, a challenge starts with 1/1,000 of the singular therapeutic dose [30, 82].

Despite a rather detailed description of the challenge technique by foreign authors, unfortunately, it is not possible to use it routinely in Russian clinical practice, as there are no legally binding Russian documents (i.e. documents protecting doctor's rights when required).

CONCLUSION

1. Adequate evaluation of clinical manifestations of allergic reactions and their association with a specific ABD, subsequent correct registration thereof in record forms or medical reports and proper provision of patients' parents or patients themselves with information on their hypersensitivity is compulsory for pediatricians and all other doctors.
2. Existence of need in registration of allergens for skin tests, at least for penicillin, in the RF.
3. Detailed clinical recommendations on diagnostics and subsequent management of patients with allergic reactions to antibiotics are in demand.
4. In the event of impossibility of skin tests and challenges in the presence of need in prescribing ABD, the preference ought to be given to drugs with the least allergic potential (e.g., macrolides).

REFERENCES

1. Ibia E. O., Schwartz R. H., Wiedermann B. L. Antibiotic rashes in children: a survey in a private practice setting. *Arch Dermatol*. 2000; 136 (7): 849–54.

2. Menniti-Ippolito G., Raschetti R., Da Cas R. et al. Active monitoring of adverse drug reactions in children. Italian Paediatric Pharmaco surveillance Multicenter Group. *Lancet*. 2000; 355: 1613–4.

3. Bourgeois F. T., Mandl K. D., Valim C. et al. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. *Pediatrics*. 2009; 124 (4): e744–50.

4. Bigby M., Jick S., Jick H. et al. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA*. 1986; 256: 3358–63.

5. Joint Task Force on Practice Parameters. Disease Management of Drug Hypersensitivity: A Practice Parameter. *Ann Allergy Asthma Immunol*. 1999; 83.

6. Langley J., Halperin S. Allergy to antibiotics in children: Perception versus reality. *Paediatr Child Health*. 2002; 7 (4): 233–7.

7. Kraemer M., Caprye-Boos H., Berman H. Increased use of medical services and antibiotics by children who claim a prior penicillin sensitivity. *West J Med*. 1987; 146: 697–700.

8. Pirmohamed M., James S., Meakin S. et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ*. 2004; 329: 15–9.

9. Solensky R., Earl H. S., Gruchalla R. S. Clinical approach to penicillin allergic patients: A survey. *Ann Allergy Asthma Immunol*. 2000; 84: 329–33.

10. Riedl M. A., Casillas A. M. Adverse drug reactions: types and treatment options. *Am Fam Physician*. 2003; 68 (9): 1781–90.

11. Karch F. E., Lasagna L. Adverse drug reactions. A critical review. *JAMA*. 1975; 234: 1236–41.

12. Johansson S. G., Bieber T., Dahl R. et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004; 113: 832–6.

13. Janeway C., Travers C., Walport M. et al. Immunology: The Immune System in Health and Disease. 5th ed. *New York: Garland*. 2001.

14. Sanz E., Boada J. Adverse drug reactions in paediatric outpatients. *Int J Clin Pharmacol Res*. 1987; 7: 169–72.

15. Woods C. G., Rylance M. E., Cullen R. E. et al. Adverse reactions to drugs in children. *BMJ*. 1987; 294: 869–70.

16. Cohen A. L., Budnitz D. S., Weidenbach K. N. et al. National surveillance of emergency department visits for outpatient adverse drug events in children and adolescents. *J Pediatr*. 2008; 152 (3): 416–21.

17. Prober C. Cepahalosporins: An update. *Pediatr Rev*. 1998; 19: 118–27.

18. Borish L. Immune mechanisms of drug allergy. *Immunol Allergy Clin North Am*. 1998; 18: 717–29.

19. Langley J., Halperin S., Bortolussi R. History of penicillin allergy and referral for skin testing: Evaluation of a pediatric program. 39th Annual Meeting of the Infectious Diseases Society of America. *San Francisco, California*. October 25–28, 2001.

20. Pichichero M. E., Pichichero D. M. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: Reliability of examination assessed by skin testing and oral challenge. *J Pediatr*. 1998; 132: 137–43.

21. Mendelson L. M., Ressler C., Rosen J. P. et al. Routine elective penicillin allergy skin testing in children and adolescents: Study of sensitization. *J Allergy Clin Immunol*. 1984; 73: 76–81.

22. Huang S. W., Borum P. R. Study of skin rashes after antibiotic use in young children. *Clin Pediatr (Phila)*. 1998; 37: 601–7.

23. Granowitz E. V., Brown R. B. Antibiotic adverse reactions and drug interactions. *Crit Care Clin*. 2008; 24: 421–42.

24. Kerr J. R. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract*. 1994; 48: 5–7.

25. Ahlstedt S. Penicillin allergy: can the incidence be reduced? *Allergy*. 1984; 39: 151–64.

26. International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet*. 1991; 337 (8753): 1308–10.

27. Lee C. E., Zembower T. R., Fotis M. A. et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med*. 2000; 160 (18): 2819–22.

28. Ponvert C., Perrin Y., Bados-Albiero A. et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol*. 2011; 22 (4): 411–8.

29. Shehab N., Patel P. R., Srinivasan A. et al. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008; 47: 735–43.

30. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010; 105 (4): 259–73.

31. Haddi E., Charpin D., Tafforeau M. et al. Atopy and systemic reactions to drugs. *Allergy*. 1990; 45 (3): 236–9.

32. Choi I. S., Han E. R., Lim S. W. Beta-lactam antibiotic sensitization and its relationship to allergic diseases in tertiary hospital nurses. *Allergy Asthma Immunol Res*. 2010; 2 (2): 114–22.

33. Patterson R., Grammer L. C., Greenberger P. A. Allergic Diseases: Diagnosis and Management. *Lippincott Williams & Wilkins*; 5th edition, 1997. 634 p.

34. Babe K. S., Serafin W. E. Histamine bradykinin, and their antagonists. In: Hardman J. G., Limbird L. E., Molinoff P. B., Ruddon R. W., eds. Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. *New York: McGraw-Hill*. 1996. P. 581–600.

35. Macy E., Poon K.-Y. T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009; 122 (8): 778 (e1–7).

36. Rosario N. A., Grumach A. S. Allergy to beta-lactams in pediatrics: a practical approach. *J Pediatr (Rio J)*. 2006; 82 (5 Suppl.): S181–8.

37. Gruchalla R. S., Pirmohamed M. Clinical practice. Antibiotic allergy. *N Engl J Med*. 2006; 354 (6): 601–9.

38. Shapiro S., Siskind V., Slone D. et al. Drug rash with ampicillin and other penicillins. *Lancet*. 1969; 2: 969–72.

39. Kearns D. L., Shira J. E., Go S. et al. Ampicillin rash in children. *Am J Dis Child*. 1973; 125: 187–290.

40. Patel B. M. Skin rash with infectious mononucleosis and ampicillin. *Pediatrics*. 1967; 40: 910–1.

41. Romano A., Di Fonso M., Papa G. et al. Evaluation of adverse cutaneous reactins to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy*. 1995; 50: 113–8.

42. Chovel-Sella A., Ben Tov A., Lahav E. et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. *Pediatrics*. 2013; 131 (5): e1424–7.

43. Stember R. H. Prevalence of skin test reactivity in patients with convincing, vague, and unacceptable histories of penicillin allergy. *Allergy Asthma Proc*. 2005; 26 (1): 59–64.

44. Solensky R., Earl H. S., Gruchalla R. S. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol*. 2000; 85 (3): 195–9.

45. Pirmohamed M., Kitteringham N. R., Park B. K. The role of active metabolites in drug toxicity. *Drug Saf*. 1994; 11: 114–44.

46. Spanou Z., Keller M., Britschgi M. et al. Involvement of drugspecific T cells in acute drug-induced interstitial nephritis. *J Am Soc Nephrol*. 2006; 17 (10): 2919–27.

47. Biuk D., Jukic T., Vukojevic N. et al. Serum sickness and uveitis. *Coll Antropol*. 2005; 29 (Suppl. 1): 127–8.

48. Schnyder B. Approach to the patient with drug allergy. *Med Clin North Am*. 2010; 94 (4): 665–79.

49. Criado P. R., Criado R. F., Avancini J. de M. et al. Drug reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug–induced Hypersensitivity Syndrome (DIHS): a review of current concepts. *An Bras Dermatol*. 2012; 87 (3): 435–49.

50. Cacoub P., Musette P., Descamps V. et al. The DRESS syndrome: a literature review. *Am J Med*. 2011; 124 (7): 588–97.

51. Peyrie`re H., Dereure O., Breton H. et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2006; 155 (2): 422–8.

52. Neuman M. G., McKinney K. K., Nanau R. M. et al. Drug-induced severe adverse reaction enhanced by human herpes virus-6 reactivation. *Transl Res*. 2013; 161 (5): 430–40.

53. Shiohara T., Inaoka M., Kano Y. Drug induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesvirus and antiviral and antidrug immune responses. *Allergol Int*. 2006; 55 (1): 1–8.

54. Roujeau J. C., Stern R. S. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994; 331 (19): 1272–85.

55. Bastuji-Garin S., Rzany B., Stern R. S. et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 1993; 129: 92–6.

56. French L. E. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int*. 2006; 55: 9–16.

57. Borchers A. T., Lee J. L., Naguwa S. M. et al. Stevens-Johnson syndrome and toxic epidermal necrolysis. *Autoimmun Rev*. 2008; 7: 598–605.

58. Thong B. Y. Update on the management of antibiotic allergy. *Allergy Asthma Immunol Res*. 2010; 2 (2): 77–86.

59. Neu H. C., Wilson A. P. R., Gruneberg R. N. Amoxycillin/Clavulanic Acid: a Review of its Efficacy in over 38,500 Patients from 1979 to 1992. *J Chemother*. 1993; 5: 67–93.

60. Thompson J. W., Jacobs R. F. Adverse effects of newer cephalosporins. An update. *Drug Saf*. 1993; 9: 132–42.

61. Norrby S. R. Side Effects of Cephalosporins. *Drugs*. 1995; 34 (Suppl. 2): 105–20.

62. Naldi L., Conforti A., Venegoni M. et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol*. 1999; 48: 839–46.

63. Mockenhaupt M., Schopf E. Progress in Allergy and Clinical Immunology, vol. 4, Cancun (Mexico): proceedings of the XVIth International Congress of Allergology and Clinical Immunology. *Cancun, Mexico*. 1997. P. 352–60.

64. Mahboob A., Haroon T. S. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol*. 1998; 37: 833–8.

65. van der Klauw M. M., Wilson J. H., Stricker B. H. Drug-associated anaphylaxis: 20 years of reporting in The Netherlands (1974–1994) and review of the literature. *Clin Exp Allergy*. 1996; 26: 1355–63.

66. Pedersen-Bjergaard U., Andersen M., Hansen P. B. Thrombocytopenia induced by noncytotoxic drugs in Denmark 1968–91. *J Intern Med*. 1996; 239: 509–15.

67. Henry D. C., Nenad R. C., Iravani A. et al. Comparison of sparfloxacin and ciprofloxacin in the treatment of communityacquired acute uncomplicated urinary tract infection in women. Sparfloxacin Multicenter Uncomplicated Urinary Tract Infection Study Group. *Clin Ther*. 1999; 21: 966–81.

68. Araujo L., Demoly P. Macrolides allergy. *Curr Pharm Des*. 2008; 14 (27): 2840–62.

69. Demoly P., Benahmed S., Valembois M. et al. Allergy to macrolide antibiotics. Review of the literature. *Presse Med*. 2000; 29 (6): 321–6.

70. Van Joost T., Dikland W., Stolz E., Prens E. Sensitization to chloramphenicol: a persistent problem. *Contact Dermatitis*. 1986; 14: 176–8.

71. Shalit I., Marks M. I. Chloramphenicol in the 1980s. *Drugs*. 1984; 28: 281–91.

72. Palchick B. A., Funk E. A., McEntire J. E., Hamory B. H. Anaphylaxis due to chloramphenicol. *Am J Med Sci*. 1984; 288: 43–5.

73. Liphshitz I., Loewenstein A. Anaphylactic reaction following application of chloramphenicol eye ointment. *Br J Ophthalmol*. 1991; 75: 64.

74. Schewach-Millet M., Shpiro D. Urticaria and angioedema due to topically applied chloramphenicol ointment. *Arch Dermatol*. 1985; 121: 587.

75. Perkins J. B., Raasch R. H. Hypersensitivity reaction following chloramphenicol administration in a patient with typhoid fever. *Drug Intell Clin Pharm*. 1987; 21: 343–5.

76. Gregoriou S., Rigopoulos D., Katsambas A. et al. Etiologic aspects and prognostic factors of patients with chronic urticaria:
nonrandomized, prospective, descriptive study. *J Cutan Med Surg*. 2009; 13: 198–203.

77. Wedi B., Raap U., Kapp A. Chronic urticaria and infections. *Curr Opin Allergy Clin Immunol*. 2004; 4: 387–96.

78. Marshall J. S. Mast-cell responses to pathogens. *Nat Rev Immunol*. 2004; 4: 787–99.

79. Eigenmann P.A. , Atanaskovic-Markovic M., J. Hourihane O'B., Lack G., Lau S., Matricardi P. M., Muraro A., Namazova Baranova L., Nieto A., Papadopoulos N. G., Rethy L.A., Roberts G., Rudzeviciene O., Wahn U., Wickman M., Host A. Testing children for allergies: why, how, who and when. An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. *Pediatric Allergy and Immunology*. 2013; 24 (2): 195–209.

80. Caubet J. C., Eigenmann P. A. Managing possible antibiotic allergy in children. *Curr Opin Infect Dis*. 2012; 25 (3): 279–85.

81. Kavadas F. D., Kasprzak A., Atkinson A. R. Antibiotic skin testing accompanied by provocative challenges in children is a useful clinical tool. *Allergy Asthma Clin Immunol*. 2013; 9 (1): 22.

82. McLean-Tooke A., Aldridge C., Stroud C. et al. Practical management of antibiotic allergy in adults. *J Clin Pathol*. 2011; 64 (3): 192–9.

83. Romano A., Gaeta F., Valluzzi R. L. et al. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics*. 2008; 122 (3): 521–7.