ISSN 1810-8830 (Print)
ISSN 2686-682X (Online)

Russian Journal of Allergy

Volume 18 • Issue 3 • 2021

RAACI
THE RUSSIAN ASSOCIATION OF ALLERGOLOGISTS AND CLINICAL IMMUNOLOGISTS

NRC INSTITUTE OF IMMUNOLOGY FMBA OF RUSSIA

PHARMARUS PRINT MEDIA

rusalljournal.ru

FOUNDERS
- Russian Association of allergologists and clinical immunologists
- National Research Center – Institute of Immunology Federal Medical-Biological Agency of Russia
- Pharmarus Print Media

PUBLISHER
Pharmarus Print Media
Address: 117246, Moscow, Nauchniy proyezd, 8 bld 7, 3rd floor, office 6
E-mail: efedks@gmail.com

EDITORIAL OFFICE
Executive editor Elena A. Philippova
Email: info@rusalljournal.ru
Phone: +7 (965) 012 70 72
Address: 117342, Moscow, Profsoyuznaya street, 69 office 1013

SUBSCRIPTION
www.rusalljournal.ru

ADVERTICEMENT
Elena Simanova
Phone: +7 (903) 512 09 37
E-mail: e.simanova@pharmaruspm.ru

INDEXATION
- Russian Science Citation Index
- Google Scholar
- Ulrich's International Periodicals Directory
- WorldCat

PUBLICATION ETHICS
Journal's ethic policies are based on:
- ICMJE
- COPE
- ORE
- CSE
- EASE

AUTHORS GUIDELINES
https://rusalljournal.ru/raj/about/submissions#authorGuidelines

TYPESET
compleate in Pharmarus Print Media
Copyeditor: *M.N. Shoshina*
Proofreader: *M.N. Shoshina*
Layout editor: *Ph.A. Ignashchenko*
Cover: *O.V. Kurenkova*

ISSN 2686-682X (Online)
ISSN 1810-8830 (Print)

Russian Journal of Allergy

Volume 18 | Issue 3 | 2021
Quarterly peer-review medical academic journal

Contents

DOI: https://doi.org/10.36691/RJA1460

Angioedema induced by angiotensin-converting enzyme inhibitors: an analysis of hospitalizations during the COVID-19 pandemic

T.M. Sabalenka[1], V.V. Zakharava[2], N.R. Prakoshyna[1]

[1] Educational Establishment Vitebsk State Order of Peoples' Friendship Medical University, Vitebsk, Republic of Belarus
[2] Vitebsk Regional Clinical Hospital, Vitebsk, Republic of Belarus

ABSTRACT

BACKGROUND: The pathogenesis of angioedema induced by angiotensin-converting enzyme inhibitors is based on the accumulation of bradykinin as a result of angiotensin-converting enzyme blockade. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 receptor, which may inhibit its production and thereby lead to an increase in bradykinin levels. Thus, SARS-CoV-2 infection may be a likely trigger for the development of angioedema.

AIMS: This study aimed to analyze cases of hospitalizations of patients with angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers during the coronavirus disease 2019 (COVID-19) pandemic.

MATERIALS AND METHODS: This study retrospectively analyzed medical records of patients admitted to the Vitebsk Regional Clinical Hospital between May 2020 and December 2020 with isolated (without urticaria) angioedema while receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In all patients, smears from the naso- and oropharynx for COVID-19 were analyzed by polymerase chain reaction.

RESULTS: Fifteen inpatients (9 men and 6 women) aged 44–72 years were admitted because of emergent events, of which 53.6% had isolated angioedema. In two cases, a concomitant diagnosis of mild COVID-19 infection was established with predominant symptoms of angioedema, including edema localized in the face, tongue, sublingual area, and soft palate. All patients had favorable disease outcomes.

CONCLUSIONS: Patients with angiotensin-converting enzyme inhibitor-induced angioedema may require hospitalization to monitor upper respiratory tract patency. There were cases of a combination of angiotensin-converting enzyme inhibitor-induced angioedema and mild COVID-19. Issues requiring additional research include the effect of SARS-CoV-2 infection on the levels of bradykinin and its metabolites, the triggering role of COVID-19 in the development of angioedema in patients receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, recommendations for the management of patients with angiotensin-converting enzyme inhibitor-induced angioedema, and a positive result for COVID-19.

Keywords: angioedema; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; bradykinin; COVID-19

For citation: Sabalenka TM, Zakharava VV, Prakoshyna NR. Angioedema induced by angiotensin-converting enzyme inhibitors: an analysis of hospitalizations during the COVID-19 pandemic. *Russian Journal of Allergy*. 2021;18(3):5–15. DOI: https://doi.org/10.36691/RJA1460

Ангиоотёки, индуцированные ингибиторами ангиотензинпревращающего фермента: анализ госпитализаций в период пандемии COVID-19

Т.М. Соболенко[1], О.В. Захарова[2], Н.Р. Прокошина[1]

[1] Витебский государственный ордена Дружбы народов медицинский университет, Витебск, Республика Беларусь
[2] Витебская областная клиническая больница, Витебск, Республика Беларусь

АННОТАЦИЯ

ОБОСНОВАНИЕ. В основе патогенеза ангиоотёков, индуцированных приёмом ингибиторов ангиотензинпревращающего фермента, лежит накопление брадикинина в результате блокады ангиотензинпревращающего фермента. Вирус SARS-CoV-2, связываясь с рецептором ангиотензинпревращающего фермента 2, возможно, подавляет его продукцию, что в свою очередь ведёт к повышению уровня брадикинина. Таким образом, инфицирование SARS-CoV-2 может являться вероятным триггером развития ангиоотёка.

ЦЕЛЬ — анализ случаев госпитализаций пациентов с ангиоотёками, ассоциированными с приёмом ингибиторов ангиотензинпревращающего фермента и блокаторов ангиотензиновых рецепторов в период пандемии COVID-19.

МАТЕРИАЛ И МЕТОДЫ. Проведён ретроспективный анализ медицинских карт стационарных пациентов, госпитализированных в Витебскую областную клиническую больницу в мае-декабре 2020 года с изолированными (без крапивницы) ангиоотёками на фоне приёма ингибиторов ангиотензинпревращающего фермента или блокаторов ангиотензиновых рецепторов. Всем пациентам были взяты мазки из носо- и ротоглотки на COVID-19 методом полимеразной цепной реакции.

РЕЗУЛЬТАТЫ. По экстренным показаниям госпитализировано 15 пациентов (9 мужчин и 6 женщин) в возрасте 44–72 лет, что составило 53,6% всех пациентов с изолированными ангиоотёками. В двух случаях установлен сопутствующий диагноз инфекции COVID-19 лёгкого течения с преобладанием в клинической картине симптомов ангиоотёка с локализацией в области лица, языка, подъязычной области, мягкого нёба. Все пациенты имели благоприятный исход заболевания.

ЗАКЛЮЧЕНИЕ. Пациенты с ангиоотёками, индуцированными ингибиторами ангиотензинпревращающего фермента, могут нуждаться в госпитализации с целью мониторинга проходимости верхних дыхательных путей. Выявлены случаи сочетания ангиоотёка на фоне приёма ингибиторов ангиотензинпревращающего фермента и инфекции COVID-19 лёгкого течения. Вопросы, требующие дополнительных исследований: влияние инфицирования SARS-CoV-2 на уровни брадикинина и его метаболитов; триггерная роль инфекции COVID-19 в развитии ангиоотёков у пациентов, получающих ингибиторы ангиотензинпревращающего фермента/блокаторы ангиотензиновых рецепторов; рекомендации по ведению пациентов с ангиоотёками, индуцированными ингибиторами ангиотензинпревращающего фермента, и положительным результатом на COVID-19.

Ключевые слова: ангиоотёк; ингибиторы ангиотензинпревращающего фермента; блокаторы ангиотензиновых рецепторов; брадикинин; COVID-19

Для цитирования: Соболенко Т.М., Захарова О.В., Прокошина Н.Р. Ангиоотёки, индуцированные ингибиторами ангиотензинпревращающего фермента: анализ госпитализаций в период пандемии COVID-19 // *Российский аллергологический журнал*. 2021. Т. 18. № 3. С. 5–15. DOI: https://doi.org/10.36691/RJA1460

Статья поступила 20.05.2021	Принята к печати 08.09.2021	Опубликована 15.09.2021
Received: 20.05.2021	Accepted: 08.09.2021	Published: 15.09.2021

Abbreviations

AE — angioedema
ACE2 — angiotensin-converting enzyme 2
AT — angiotensin
ARB — angiotensin receptor blockers
BK — bradykinin
ACEi — angiotensin-converting enzyme inhibitors
HAE — hereditary angioedema
PCR — polymerase chain reaction
RAAS — renin-angiotensin-aldosterone system

Background

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) rank high in treating arterial hypertension and chronic heart failure. In addition, they are used to preserve renal function in patients with diabetes mellitus and chronic kidney disease. About 40 million people worldwide use ACE inhibitors, and the widespread use of this group of drugs has led to an increase in the prevalence of adverse drug reactions [1, 2].

Angioedema (AE) can generate potential life-threatening side effects in 0.1–0.7% of individuals receiving ACE inhibitors and somewhat less frequently while taking ARBs (0.1%) [3]. Among all cases of AE requiring hospitalization in the emergency department, the proportion of ACEi-induced AE is 30–40% [4, 5]. According to our data, 44.8% of patients (total patients = 87) of the Vitebsk Regional Clinical Hospital were hospitalized for emergency indications with isolated AE in 2012 and had the reaction caused by the intake of ACE inhibitors [6]. Among patients seeking emergency care, up to 16% of patients required intubation, and 1% needed a tracheostomy. Rapid onset of symptoms, involvement of the tongue, soft palate or larynx, symptoms of salivation, and respiratory distress are associated with a higher risk of intubation [7].

AE caused by ACE inhibitors belongs to acquired bradykinin-mediated AE, and the vasodilating peptide bradykinin (BK) plays a key role in their pathogenesis. ACE inhibitors provide a decrease in the formation of angiotensin (AT) II and prevent the conversion of BK

into inactive metabolites, leading to its accumulation [8]. BK is also expected to participate in the development of AE when taking ARB [9, 10]. Thus, according to experimental data, one of the consequences of the blockade of AT1 receptors is a reactive increase in AT-II formation. The effect of AT-II on AT2 receptors leads to an increase in the BK level [9].

New drugs are being introduced into clinical practice that affect the renin-angiotensin-aldosterone system (RAAS) and can affect the BK metabolism, in particular, the neprilysin inhibitor sacubitril (used in fixed combination with valsartan), hypoglycemic drugs of the class of dipeptidyl peptidase 4 inhibitors (DPP4) [11]. BK is a nonapeptide that is cleaved from high molecular weight kininogen by plasma kininogenase. Its biological effect is implemented by activating B2 receptors located in the membranes of endothelial and smooth muscle cells. The resulting BK is rapidly inactivated by enzymatic degradation, mainly under the action of kininase II (ACE), as well as neutral endopeptidase (neprilysin) and DPP4. In addition, Carboxypeptidase N (kininase I) and aminopeptidase P (APP) catabolizes BK, forming partially active products. Angiotensin-converting enzyme 2 (ACE2) is involved in the cleavage of the BK active metabolite des-Arg9-bradykinin [2, 5]. It has also been revealed that polymorphism of genes encoding the corresponding molecules involved in the metabolism and action of BK (APP, DPP4, B2 receptor, etc.) may play a role in the development of AE when taking an ACE inhibitor. An elevated local level of BK leads to increased release of nitric oxide and prostaglandins. This enhances the vascular permeability in the postcapillary and venular regions with extravasation of fluid and the development of edema [2].

ACEi-induced AEs are pale, not itchy, not accompanied by urticaria, and are often localized in the region of the lips, tongue, pharynx, and larynx. The rare localization of AE also includes the abdominal organs. Edema can develop at different times from the beginning of the use of ACE inhibitors. Risk factors include African American origin, female gender, old age, smoking, and seasonal allergies. AE can resolve spontaneously. However, the continued use of ACE inhibitors can cause a relapse [5, 11]. After discontinuation of ACE inhibitors, the probability of AE recurrence remains approximately for 6 weeks by suppressing the tissue ACE. During this period, prescription drugs that reduce the RAAS activity to patients are not recommended [11]. In patients with ACEi-induced AE, the risk of such an adverse reaction when substituted for ARB is lower than 10% (0 – 17%) [12].

Patients with ACEi-induced AE require timely diagnostics and emergency care with correction of therapy to prevent recurrent episodes. The diagnosis is established based on anamnesis, clinical presentation, ruling out of histamine, and other types of bradykinin AE [5]. In the case of suspected AE caused by the intake of ACEi/ARB, these classes of drugs should be immediately stopped and, if necessary, replaced by drugs of other pharmacological groups. After discontinuation of ACE inhibitors/ARB, edema usually resolves spontaneously within 48–72 hours [2]. Patients with AE localization on the face, neck, tongue, and larynx must be examined by an otorhinolaryngologist to assess the patency of the glottis and upper respiratory tract. The signs of obstruction such as inability to swallow, salivation, stridor, cyanosis, accessory muscle involvement in breathing, nasotracheal intubation or tracheotomy/conicotomy should also be examined promptly. Patients with AE of the tongue and larynx require follow-up in the intensive care unit [2, 13].

Standard treatment for the relief of AE caused by mast cell mediators includes administering antihistamines, systemic glucocorticoids, and, in severe cases, epinephrine. However, with ACEi-induced AE, this therapy is not pathogenetically justified and might be ineffective [14]. In this regard, to relieve AE caused by the intake of ACE inhibitors, a therapy aimed at BK, approved for the treatment of acute attacks of hereditary AE (HAE) was proposed. The therapy includes a blocker of BK type 2 receptors icatibant, an inhibitor of human C1-esterase, and fresh frozen plasma. Currently, the advantages of this approach in the treatment of ACEi-induced AE are insufficiently proven and require further investigations [2]. In a randomized controlled trial, M. Baş et al. [15] showed a faster resolution of the symptoms of ACEi-induced AE when using icatibant compared with standard therapy with prednisolone and clemastine. However, the efficacy of icatibant has not been confirmed in two other randomized trials evaluating its effect compared with placebo [16, 17]. In the occurrence of AE in patients receiving an ACE inhibitor (especially for a long time), various triggers are of great importance. Among the drugs that can contribute to the development of AE during the intake of ACE inhibitors, nonsteroidal anti-inflammatory drugs, calcium antagonists, DPP4 inhibitors, mTOR inhibitors (mammalian target of rapamycin), and other immunosuppressants are indicated.

Trauma, surgical manipulations in the head or neck area can be a provoking factor [2, 5, 8]. It is assumed that COVID-19 infection may also trigger the development of AE in patients receiving ACE inhibitors [18]. The SARS-CoV-2 virus, by binding to the ACE2 receptor, possibly suppresses the production of ACE2, which in turn leads to an increase in the BK level [19]. Cases of isolated AE have been described in patients infected with SARS-CoV-2 and receiving ACE inhibitors [18, 20, 21].

The work aimed to analyze the cases of hospitalizations of patients with AE associated with the intake of an ACE inhibitor or ARB during the COVID-19 pandemic.

Materials and methods

Study design

An observational single-center retrospective continuous controlled study was conducted, which included a comparative analysis of the medical records of patients

hospitalized during the COVID-19 pandemic with AE caused by the intake of ACE inhibitors/ARB, with cases of isolated AE from other causes.

Inclusion criteria

The inclusion criteria were an established diagnosis of AE.

Exclusion criteria were a combination of AE and urticaria, established diagnosis of HAE; family history of a confirmed diagnosis of HAE.

Conditions of conducting

The study was conducted in the Vitebsk Regional Clinical Hospital (VRCH, Republic of Belarus). During the study period, the patients aged 18 years and older with emergency allergic pathology were hospitalized at the VRCH.

Study duration

The enrollment period of the study was from May to December 2020. Therefore, there was no offset of the scheduled timeslots.

Description of the medical intervention

The study was performed using a continuous sample of medical records of patients treated in intensive care units and allergy departments of the Vitebsk Regional Clinical Hospital with isolated (without urticaria) AE from May to December 2020. Upon admission to the hospital, all patients underwent a mandatory laboratory study of biomaterial (nasopharyngeal and oropharyngeal swabs) for the presence of concomitant COVID-19 infection using the real-time polymerase chain reaction (RT-PCR) method. For further analysis, the study group included medical records of patients who received ACE inhibitors/ARB and did not have other obvious causes of the development of AE. The Naranjo algorithm was used to establish a causal relationship between the development of AE and the use of ACE inhibitors/ARB [22]. The control group included patients with isolated AE but not associated with the intake of an ACE inhibitor/ARB.

Main study outcome

Clinical and anamnestic data and laboratory and instrumental examinations of AE patients while taking ACE inhibitors/ARB were evaluated.

Additional study outcomes

Causative ACE inhibitors and ARB were analyzed.

Subgroup analysis

Hospitalized patients with isolated AE were distributed into two groups: patients with an ACEi/ARB-induced AE and a comparison group consisting of patients with AE but not associated with the intake of ACE inhibitors/ARB.

Outcome registration methods

Analysis of indicators entered into the database from medical records of hospital patients included demographic indicators (gender, age); the main clinical diagnosis and concomitant diseases; AE localization; hospitalization in the intensive care unit; causative ACE inhibitors/ARB and concomitant medications; anamnestic data (episodes of AE, history of atopy, family history of AE); data of basic laboratory (complete blood count, biochemical blood test, coagulogram) and instrumental (chest X-ray, electrocardiogram) studies; the results of a qualitative determination of IgG/IgM to SARS-CoV-2 in blood serum and swabs from the nasopharynx and oropharynx for COVID-19 by PCR.

Ethical considerations

The Committee approved the study design on the Ethics of Clinical Trials of the Vitebsk State Order of Friendship of Peoples Medical University, protocol No. 7 dated 02.12.2020.

Statistical analysis

Principles for calculating the sample size. The sample size was not pre-calculated.

Statistical data analysis methods included Statistica 10.0 software (StatSoft Inc., USA) and Microsoft Office Excel 2016 (Microsoft Corporation, USA) for data processing. The median (25–75% interquartile range) of the patients' age was calculated as Me (25; 75); the Mann–Whitney test determined the significance of differences in quantitative indicators. The two-tailed Fisher's exact test determined the frequency of qualitative features. The results were considered to be statistically significant at $p < 0.05$.

Results

Objects (participants) of the study

In the study, we retrospectively assessed the medical records of 28 patients hospitalized for emergency indications at the VRCH from May to December 2020 with isolated AE. The group of patients with ACEi/ARB-induced AE included 15 patients (9 men and 6 women) who received treatment with ACE inhibitors/ARB and had no other obvious causes of the development of AE. The share of AEs caused by intake of ACEi/ARB was 53.6%. According to the Naranjo algorithm, a causal relationship with the intake of ACE inhibitors/ARB was determined as probable in 12 patients (80%) and as possible in 3 patients (20%). The patients were 44–72 years old; *Me* 59 (55; 62) years old. The comparison group included 13 patients (6 men and 7 women) aged 19–72 years; 47 (34; 62) years old. The difference in age with the ACEi/ARB-induced AE group was statistically insignificant ($p = 0.19$). Thus, in the comparison group, AE was caused by drugs in 4 out of 13 cases, by food in 1 out of 13 cases; and in 8 out of 13 patients, the cause of AE has not been established.

Key research findings

The characteristics of patients with ACEi/ARB-induced AE are presented in Table 1.

 DOI: https://doi.org/10.36691/RJA1460

The localization of edema was noted in the face, tongue, and soft palate (Fig. 1). Peripheral AE was not found either in the study group or in the comparison group. The frequency of admissions to the intensive care unit of AE patients while taking an ACEi/ARB was 20% (3/15) and did not differ significantly from the group of patients with isolated AE, not associated with intake of an ACEi/ARB (4/13); $p = 0.67$. In the study group, repeated episodes of AE were noted in 9/15 patients, including in 3 cases associated with repeated use of ACE inhibitors; 2 patients out of 15 had atopy/bronchial asthma in history; family history of AE was absent. All patients received an ACEi/ARB for arterial hypertension; monotherapy was used in 7 out of 15 cases, combination therapy was used in 5 cases out of 15, and 3 out of 15 patients used ACE inhibitors irregularly. The majority (13; 86.7%) of patients had concomitant chronic diseases, and in 53.3% of cases, they took drugs from other groups together with antihypertensive drugs. In the comparison group, 6 out of 13 patients had AE in the history; 3 out of 13 patients had concomitant atopy or bronchial asthma; in 1 case out of 13, a family history of AE was indicated; concomitant chronic diseases were noted in 11 (84.6%) cases. The level of C-reactive protein was determined in 23 out of 28 patients. An increase in C-reactive protein level was found in 43% of cases in the ACEi/ARB-induced AE group and 22% of cases in the comparison group ($p = 0.39$). The level of the C4 component of complement in the studied medical records was not determined.

Nasopharyngeal and oropharyngeal swabs were taken from all patients for COVID-19 by PCR. A qualitative method performed the determination of IgG/IgM to SARS-CoV-2 by 23 (82%) patients. In the group of patients with ACEi/ARB-induced AE, IgG/IgM was

Table 1. Characteristics of patients with angioedema induced by angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Localization of AE	ICU	ACEi/ ARB	Mode of application	Concomitant drugs	AE episodes in the history	IgG/IgM to SARS-COV2	PCR
Tongue, soft palate uvula, lips, cheek	Yes	Captopril + Lisinopril	Single intake	No	Yes /Lisinopril	negative	negative
Lips, cheek	No	Lisinopril	Regular intake for 4 years	No	No	negative	negative
Cheek	No	Enalapril	1 week	Yes	Yes /Lisinopril	-	negative
Lip, cheek	No	Enalapril	Regular intake	Yes	Yes /Enalapril	negative	negative
Face, tongue	No	Enalapril	Regular intake	Yes	Yes	-	positive
Tongue, soft palate, sublingual region	Yes	Enalapril	Regular intake For 6 months	Yes	No	negative.	positive
Face, tongue	No	Losartan	Regular intake	No	Yes	negative	negative
Lips, cheek	No	Enalapril	Regular intake	No	Yes	negative	negative
Face	No	Perindopril	Regular intake	Yes	Yes	IgM positive IgG positive	negative
Tongue	No	Losartan	Regular intake	Yes	No	IgM positive IgG p positive	negative
Soft palate uvula	No	Captopril	Single intake	Yes	Yes	negative	negative
Tongue	Yes	Captopril	Single intake	No	No	negative	negative
Soft palate uvula	No	Captopril + Losartan	Regular intake of Losartan	Yes	No	negative	negative
Lips	No	Lisinopril	Regular intake	Yes	Yes	IgM negative IgG positive	negative
Face	No	Losartan	Regular intake	No	No	-	negative

Note. AE — angioedema; ICU — intensive care unit; ACEi — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; D — drugs; PCR — a polymerase chain reaction.

 DOI: https://doi.org/10.36691/RJA1460

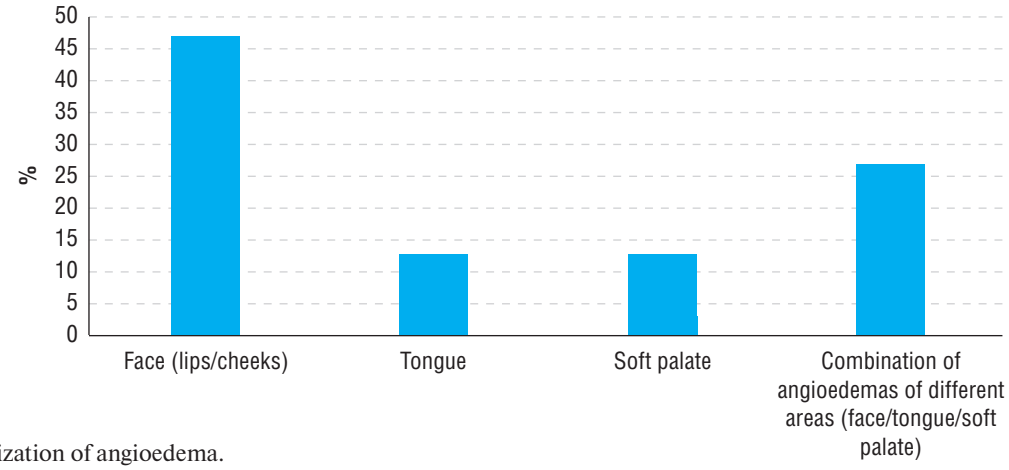

Fig. 1. Localization of angioedema.

determined in 12 cases out of 15. The positive result of IgG to SARS-CoV-2 was detected in 1 case, and those of IgG and IgM were revealed in 2 cases (PCR test result was negative). In 2 cases, a positive PCR test result was obtained, and a concomitant COVID-19 infection was diagnosed. Patients with AE and COVID-19 did not increase body temperature, changes on a chest X-ray, or a decrease in the oxygen level in the blood; there was only an increase in C-reactive protein level and 1 case an increase in the level of D-dimer. AE was localized on the face, tongue, sublingual region, and soft palate.

In the comparison group, the determination of IgG/IgM to SARS-CoV-2 was performed in 11 cases out of 13. Positive IgG results were registered in 2 cases, that of IgM was revealed in 1 case, and those of IgG and IgM were registered in 1 case (PCR test result was negative). In addition, a positive PCR test result was obtained in 1 patient with lip and cheek AE of unclear etiology, and a simultaneous diagnosis of asymptomatic COVID-19 infection was established.

Treatment of AE included parenteral administration of systemic glucocorticoid (dexamethasone), H_1-antihistamines (clemastine, chloropyramine), and, in some cases, furosemide. In AE patients, while taking ACE inhibitors/ARB, these groups of drugs were cancelled. If basic arterial hypertension therapy was required, they were replaced with antihypertensive drugs from the calcium antagonists and/or thiazide-like diuretics group. All patients had a favorable outcome of AE.

Additional research outcomes

The distribution of patients depending on the type of causative ACE inhibitor/ARB is presented in Fig. 2. The most common causes of AE development were enalapril and captopril. In 2 cases, long-acting ACEi and ARB were used in conjunction with captopril.

Discussion

Summary of the main research outcome

ACEi-induced AE can have life-threatening localization and require hospitalization. An infection caused by SARS-CoV-2 is discussed as a possible trigger for developing this type of AE. In our study, cases of a combination of AE during the intake of an ACE inhibitor and a mild COVID-19 infection were revealed.

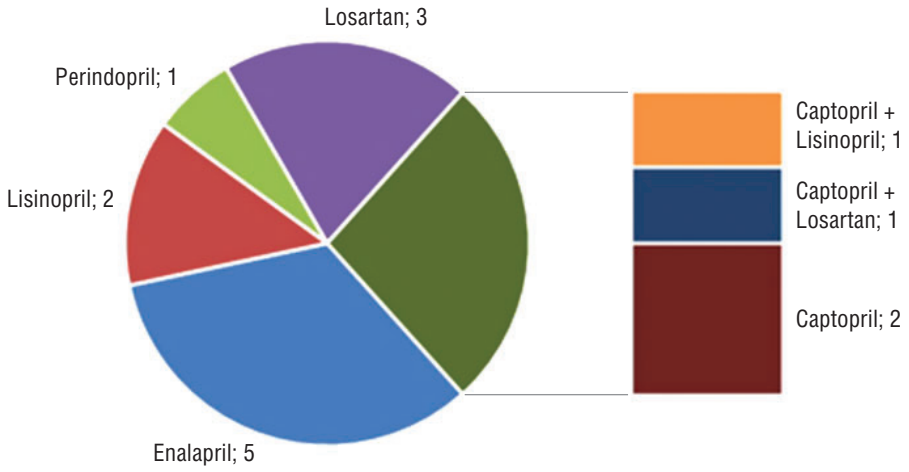

Fig. 2. Causal angiotensin-converting enzyme inhibitors / angiotensin receptor blockers.

 DOI: https://doi.org/10.36691/RJA1460

Discussion of the main research outcome

AE induced by intake of an ACE inhibitor can obstruct the upper airway and lead to asphyxia. The diagnosis of ACEi-induced AE is established based on clinical and anamnestic data, and there are no diagnostic tests to confirm it. Until now, there is no approved approach of drug therapy for this type of bradykinin AE. Thus, the analysis of clinical characteristics, management approach, and possible trigger factors of AE caused by ACE inhibitors/ARB is important for improving the diagnostics, treatment, and prevention of the development of this potentially life-threatening adverse reaction. Intake of an ACE inhibitor is one of the most common causes of developing isolated AE that requires urgent care [4]. In our study, AE patients taking ACE inhibitors/ARB accounted for about half of all hospitalization cases for isolated AE. According to the literature, risk factors for ACEi-induced AE are over 65 years and female gender [5]. In this study, the median age of patients with AE caused by ACE inhibitors/ARB was 59 years; distribution by gender showed some predominance of men (60%), and such results may be associated with the small size of the study group. Comparable data are presented in the recently published work by A. Pfaue et al. [23]. A retrospective analysis of medical records of patients hospitalized with isolated AE in the otorhinolaryngology department was conducted. The proportion of patients with AE caused by drugs blocking the RAAS (ACE inhibitors, ARB, and renin inhibitors) was 41% (84 out of 203 patients), the average age was 71 years (43–94 years), and the ratio of women to men was 48% and 52%, respectively.

According to our data, enalapril and captopril caused most commonly the development of drug-induced AE, which is associated not with the peculiarities of these molecules but with the frequency of their use. Furthermore, in various studies, the ratio of causative ACE inhibitors/ARB differed depending on the region and the time of their conduct [1, 23, 24].

Localization of AE in the face and oral cavity, established in our study, is typical for this type of AE. With isolated AE of the soft palate uvula, which was noted in 2 cases, differential diagnostics with uvula edema is required due to snoring (taking into account the presence of snoring, sleep disturbances, apnea) [23]. Life-threatening localization of AE, which required hospitalization in the intensive care unit, was established in 20% of patients.

There were no cases of intubation and tracheostomy. A favorable outcome in all cases analyzed was probably due to the timely cancellation of ACE inhibitors/ARB or the independent resolution of AE. The small size of the study group should also be considered. In a study by A. Pfaue et al. [23], the risk of emergency intubation and/or tracheostomy was 9 times higher in patients with AE caused by drugs blocking the RAAS compared with patients with AE induced by other causes (odds ratio 9.077; 95% CI 1.072–76.859). The authors emphasize the importance of doctors who work in emergency departments about the clinical presentation and aspects of therapy for this type of AE [23].

In the study group of patients with ACEi/ARB-induced AE, there was a rather high frequency of repeated episodes (60%), including those associated with repeated intake of ACE inhibitors. Recurrent AE in patients receiving ACEi/ARB may indicate a lack of awareness among doctors about this adverse reaction. The problem of underestimating general practitioners (therapists) of the possibility of bradykinin-mediated AE during therapy with ACE inhibitors is discussed in a recent study by L. Mihaela et al. [24].

The inpatient records we studied also contained indications of the facts of self-medication, which is associated with the possibility of over-the-counter sale of such drugs as captopril, enalapril, and lisinopril. When establishing the diagnosis of AE caused by intake of an ACEi/ARB, it is important to inform the patient about the possibility of a recurrence of edema, despite the cancellation of an ACEi/ARB, and the need to seek emergency help in this case, as well as to explain the danger of self-medication. In addition, it should be borne in mind that ACE inhibitors/ARB can be trigger factors in HAE, acquired AE with deficiency or impairment of the functional activity of the C1 inhibitor, and idiopathic AE. In a study by Z. Balla et al. [25], out of 149 patients with recurrent AE, while taking an ACE inhibitor, 2 patients and 12 other family members were diagnosed with HAE with C1 inhibitor deficiency. In 3 cases, acquired C1 inhibitor deficiency was detected. HAE without C1-inhibitor deficiency is a rare form that, in its clinical presentation, may be similar to ACEi-induced AE, but a family history of AE is typical in it. In this case, genetic testing is required to confirm the diagnosis. In the Republic of Belarus, in the presence of clinical and anamnestic data, the C4 component of complement is determined as a screening for HAE, at the republican level, both immunological (measurement of the levels of C4, C1 inhibitor, C1q, determination of the functional activity of C1 inhibitor) and genetic studies (sequencing the genes *SERPING1*, *FXII*, *ANGPT1*, *PLG*, etc.) are performed [26]. According to the medical records we analyzed, there were no referral cases of patients to republican centers for HAE diagnostics. Patients with relapses of AE need further follow-up and additional examination at the outpatient stage, if necessary.

We were unable to estimate the period from the beginning of intake of an ACE inhibitor to the onset of AE due to insufficient information in the medical documentation. According to the literature, the development of AE is possible both in the early terms (first weeks) and several years after the start of therapy [3]. In a retrospective cohort study by A. Banerji et al. [1], which included 134,945 patients who received an ACE inhibitor, in 0.7% cases, an ACE inhibitor-induced AE developed during the first 5 years of administration. In only 10% of them, AE occurred in month 1 of therapy. The possibility of AE development during the long-

term therapy with ACE inhibitors/ARB complicates the diagnostics, and the factors contributing to the development of AE often remain unclear. Studies have been published in which an increase in C-reactive protein level was noted in AE induced by ACE inhibitors/ARB. In addition, the role of inflammatory stimuli in the emergence or maintenance of AE in some patients was suggested [23, 27].

In December 2019, an epidemic of a new infectious disease called COVID-19 began in China, caused by a representative of the coronavirus family, SARS-CoV-2, which spread worldwide. Endothelial dysfunction and increased vascular permeability are characteristic pathological signs of COVID-19 [28]. These phenomena can lead to increased fluid extravasation and increased risk of AE. The protective effects of ACE inhibitors/ARB are believed to be associated with an increase in the expression of ACE2 and inhibition of excessive RAAS activity through a decrease in the effects of AT-II. The binding of SARS-CoV-2 to the ACE2 receptor can lead to suppression of surface regulation of ACE2, thereby reducing its protective effects and aggravating the adverse effects of AT-II. A decrease in ACE2 expression disrupts its role in the cleavage of several substrates, including BK metabolites [18, 28].

In the described cases of the development of AE during the intake of ACE inhibitors and COVID-19 infection, the new coronavirus infection is considered a possible trigger factor. Infection with SARS-CoV-2 can be a "second blow" that leads to edema in patients receiving this group of drugs. Management approach consisted in cessation of an ACE inhibitor; in addition, in 2 cases, systemic glucocorticoids and antihistamines were used [20, 21], and in 1 case, tranexamic acid was used [18]. A case of urticaria with AE as a premonitory symptom of COVID-19 infection has also been published. The role of histamine and BK in the development of AE, in this case, is discussed [29]. The course of COVID-19 infection is highly variable. In the analyzed cases of the combination of ACEi-induced AE and COVID-19, the symptoms of AE prevailed in the clinical presentation. The signs of an upper respiratory tract infection (rhinitis, sore throat) were probably concealed by symptoms of edema of the oropharyngeal mucous membrane. In the comparison group, a case of a combination of isolated AE of the lips and a face with an asymptomatic course of COVID-19 was established.

Study limitations

The limitations of this study were its retrospective nature and the short duration of the period analyzed.

Conclusion

Due to their proven efficacy in treating many cardiovascular diseases, ACE inhibitors and ARB are widely used in clinical practice. However, until now, AE caused by intake of ACEi/ARB remains a complication of pharmacotherapy, which is difficult to diagnose, with insufficiently studied mechanisms of formation and approaches to treatment. Patients with ACEi-induced AE may require hospitalization to monitor the patency of the upper airway. The most common causes of drug-induced AE among the analyzed cases were enalapril and captopril. In patients with AE, while taking ACE inhibitors, cases of mild COVID-19 infection were revealed with a predominance of AE symptoms in the clinical presentation with localization in the face, tongue, sublingual region, and soft palate.

With the development of AE, a targeted collection of anamnesis is required regarding the use of ACEi/ARB and the symptoms of COVID-19, as well as PCR examination for COVID-19 infection.

Questions requiring further research include the effect of infection with SARS-CoV-2 on the levels of BK and its metabolites; the triggering role of COVID-19 infection in the development of AE in patients receiving ACEi/ARB; recommendations for the management of patients with ACEi-induced AE and a positive result for COVID-19.

Additional information

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare no obvious and potential conflicts of interest related to the publication of this article.

Authors' contribution. T.M. Sabalenka, V.V. Zakharava — research concept and design, collection and processing of material; T.M. Sabalenka, N.R. Prakoshyna — statistical data processing, editing; T.M. Sabalenka, N.R. Prakoshyna, V.V. Zakharava — text writing. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. Banerji A, Blumenthal K, Lai K, Zhou L. Epidemiology of ACE inhibitor angioedema utilizing a large electronic health record. *J Allergy Clin Immunol Pract*. 2017;5(3):744–749. doi: 10.1016/j.jaip.2017.02.018
2. Montinaro V, Cicardi M. ACE inhibitor-mediated angioedema. *Int Immunopharmacol*. 2020;78:106081. doi: 10.1016/j.intimp.2019.106081
3. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: A review of the literature. *J Clin Hypertens (Greenwich)*. 2017;19(12):1377–1382. doi: 10.1111/jch.13097
4. Banerji A, Clark S, Blanda M, et al. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. *Ann Allergy Asthma Immunol*. 2008;100(4):327–332. doi: 10.1016/s1081-1206(10)60594-7

5. Kostis W, Shetty M, Chowdhury Y, Kostis J. ACE inhibitor-induced angioedema: a review. *Curr Hypertens Rep*. 2018;20(7):55. doi: 10.1007/s11906-018-0859-x
6. Sobolenko TM, Vykhristenko LR. Angioedema associated with treatment of angiotensin converting enzyme inhibitors. *Meditsinskie novosti*. 2014;(6):6–8. (In Russ).
7. Kieu M, Bangiyev J, Thottam P, Levy P. Predictors of airway intervention in angiotensin-converting enzyme inhibitor–induced angioedema. *Otolaryngol Head Neck Surg*. 2015;153(4):544–550. doi: 10.1177/0194599815588909
8. Gill P, Betschel S. The clinical evaluation of angioedema. *Immunol Allergy Clin North Am*. 2017;37(3):449–466. doi: 10.1016/j.iac.2017.04.007
9. Irons B, Kumar A. Valsartan-induced angioedema. *Ann Pharmacother*. 2003;37(7-8):1024–1027. doi: 10.1345/aph.1c520
10. Shino M, Takahashi K, Murata T, et al. Angiotensin II receptor blocker-induced angioedema in the oral floor and epiglottis. *Am J Otolaryngol*. 2011;32(6):624–626. doi: 10.1016/j.amjoto.2010.11.014
11. Stone C, Brown N. Angiotensin-converting enzyme inhibitor and other drug-associated angioedema. *Immunol Allergy Clin North Am*. 2017;37(3):483–495. doi: 10.1016/j.iac.2017.04.006
12. Knecht S, Dunn S, Macaulay T. Angioedema related to angiotensin inhibitors. *J Pharm Pract*. 2014;27(5):461–465. doi: 10.1177/0897190014546101
13. Long BJ, Koyfman A, Gottlieb M. Evaluation and management of angioedema in the emergency department. *West J Emerg Med*. 2019;20(4):587–600. doi: 10.5811/westjem.2019.5.42650
14. Cicardi M, Aberer W, Banerji A, et al.; HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69(5):602–616. doi: 10.1111/all.12380
15. Baş M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med*. 2015;372(5):418–425. doi: 10.1056/NEJMoa1312524
16. Straka BT, Ramirez CE, Byrd JB, et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2017;140(1):242–248. doi: 10.1016/j.jaci.2016.09.051
17. Sinert R, Levy P, Bernstein JA, et al.; CAMEO study group. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. *J Allergy Clin Immunol Pract*. 2017;5(5):1402–1409. doi: 10.1016/j.jaip.2017.03.003
18. Grewal E, Sutarjono B, Mohammed I. Angioedema, ACE inhibitor and COVID-19. *BMJ Case Rep*. 2020;13(9):e237888. doi: 10.1136/bcr-2020-237888
19. Chung M, Karnik S, Saef J, et al. SARS-CoV-2 and ACE2: the biology and clinical data settling the ARB and ACEI controversy. *EBioMedicine*. 2020;58:102907. doi: 10.1016/j.ebiom.2020.102907
20. Cohen A, DiFrancesco M, Solomon S, Vaduganathan M. Angioedema in COVID-19. *Eur Heart J*. 2020;41(34):3283–3284. doi: 10.1093/eurheartj/ehaa452
21. Kuzemczak M, Kavvouras C, Alkhalil M, Osten M. ACE inhibitor-related angioedema in a COVID-19 patient—a plausible contribution of the viral infection? [letter]. *Eur J Clin Pharmacol*. 2021. doi: 10.1007/s00228-020-03082-w
22. Naranjo C, Busto U, Sellers E, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245. doi: 10.1038/clpt.1981.154
23. Pfaue A, Schuler PJ, Mayer B, et al. Clinical features of angioedema induced by renin-angiotensin-aldosterone system inhibition: a retrospective analysis of 84 patients. *J Community Hosp Intern Med Perspect*. 2019;9(6):453–459. doi: 10.1080/20009666.2019.1698259
24. Mihaela LP, Florin AV, Bocsan C, et al. Acquired angioedema induced by angiotensin-converting enzyme inhibitors — experience of a hospital-based allergy center. *Exp Ther Med*. 2020;20(1):68–72. doi: 10.3892/etm.2020.8474
25. Balla Z, Zsilinszky Z, Pólai Z, et al. The importance of complement testing in acquired angioedema related to angiotensin-converting enzyme inhibitors. *J Allergy Clin Immunol Pract*. 2021;9(2):947–955. doi: 10.1016/j.jaip.2020.08.052
26. Guryanova IE, Zharankova YuS, Polyakova EA, et al. Molecular genetic diagnosis of hereditary angioedema. *Proceedings of the National Academy of Sciences of Belarus. Medical series*. 2021;18(1):25–35. (In Russ). doi: 10.29235/1814-6023-2021-18-1-25-35
27. Bas M, Hoffmann TK, Bier H, Kojda G. Increased C-reactive protein in ACE-inhibitor-induced angioedema. *Br J Clin Pharmacol*. 2005;59(2):233–238. doi: 10.1111/j.1365-2125.2004.02268.x
28. Guzik T, Mohiddin S, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*. 2020;116(10):1666–1687. doi: 10.1093/cvr/cvaa106
29. Hassan K. Urticaria and angioedema as a prodromal cutaneous manifestation of SARS-CoV-2 (COVID-19) infection. *BMJ Case Rep*. 2020;13(7):e236981. doi: 10.1136/bcr-2020-236981

ЛИТЕРАТУРА

1. Banerji A., Blumenthal K.G., Lai K.H., Zhou L. Epidemiology of ACE inhibitor angioedema utilizing a large electronic health record // J Allergy Clin Immunol Pract. 2017. Vol. 5, N 3. P. 744–749. doi: 10.1016/j.jaip.2017.02.018
2. Montinaro V., Cicardi M. ACE inhibitor-mediated angioedema // Int Immunopharmacol. 2020. Vol. 78. P. 106081. doi: 10.1016/j.intimp.2019.106081
3. Brown T., Gonzalez J., Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: a review of the literature // J Clin Hypertens (Greenwich). 2017. Vol. 19, N 12. P. 1377–1382. doi: 10.1111/jch.13097
4. Banerji A., Clark S., Blanda M., et al. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department // Ann Allergy Asthma Immunol. 2008. Vol. 100, N 4. P. 327–332. doi: 10.1016/S1081-1206(10)60594-7
5. Kostis W.J., Shetty M., Chowdhury Y.S., Kostis J.B. ACE inhibitor-induced angioedema: a review // Curr Hypertens Rep. 2018. Vol. 20, N 7. P. 55. doi: 10.1007/s11906-018-0859-x
6. Соболенко Т.М., Выхристенко Л.Р. Ангионевротический отек при лечении ингибиторами ангиотензин-превращающего фермента // Медицинские новости. 2014. № 6. С. 6–8.
7. Kieu M.C., Bangiyev J.N., Thottam P.J., Levy P.D. Predictors of airway intervention in angiotensin-converting enzyme inhibitor-induced angioedema // Otolaryngol Head Neck Surg. 2015. Vol. 153, N 4. P. 544–550. doi: 10.1177/0194599815588909
8. Gill P., Betschel S.D. The Clinical evaluation of angioedema // Immunol Allergy Clin North Am. 2017. Vol. 37, N 3. P. 449–466. doi: 10.1016/j.iac.2017.04.007

9. Irons B.K., Kumar A. Valsartan-induced angioedema // Ann Pharmacother. 2003. Vol. 37, N 7-8. P. 1024–1027. doi: 10.1345/aph.1C520
10. Shino M., Takahashi K., Murata T., et al. Angiotensin II receptor blocker-induced angioedema in the oral floor and epiglottis // Am J Otolaryngol. 2011. Vol. 32, N 6. P. 624–626. doi: 10.1016/j.amjoto.2010.11.014
11. Stone C.Jr., Brown N.J. Angiotensin-converting enzyme inhibitor and other drug-associated angioedema // Immunol Allergy Clin North Am. 2017. Vol. 37, N 3. P. 483–495. doi: 10.1016/j.iac.2017.04.006
12. Knecht S.E., Dunn S.P., Macaulay T.E. Angioedema related to angiotensin inhibitors // J Pharm Pract. 2014. Vol. 27, N 5. P. 461–465. doi: 10.1177/0897190014546101
13. Long B.J., Koyfman A., Gottlieb M. Evaluation and management of angioedema in the emergency department // West J Emerg Med. 2019. Vol. 20, N 4. P. 587–600. doi: 10.5811/westjem.2019.5.42650
14. Cicardi M., Aberer W., Banerji A., et al.; HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group // Allergy. 2014. Vol. 69, N 5. P. 602–616. doi: 10.1111/all.12380
15. Baş M., Greve J., Stelter K., et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema // N Engl J Med. 2015. Vol. 327, N 5. P. 418–425. doi: 10.1056/NEJMoa1312524
16. Straka B.T., Ramirez C.E., Byrd J.B., et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema // J Allergy Clin Immunol. 2017. Vol. 140, N 1. P. 242–428. doi: 10.1016/j.jaci.2016.09.051
17. Sinert R., Levy P., Bernstein J.A., et al.; CAMEO study group. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema // J Allergy Clin Immunol Pract. 2017. Vol. 5, N 5. P. 1402–1409. doi: 10.1016/j.jaip.2017.03.003
18. Grewal E., Sutarjono B., Mohammed I. Angioedema, ACE inhibitor and COVID-19 // BMJ Case Rep. 2020. Vol. 13, N 9. P. e237888. doi: 10.1136/bcr-2020-237888
19. Chung M.K., Karnik S., Saef J., et al. SARS-CoV-2 and ACE2: the biology and clinical data settling the ARB and ACEI controversy // EBioMedicine. 2020. Vol. 58. P. 102907. doi: 10.1016/j.ebiom.2020.102907
20. Cohen A.J., DiFrancesco M.F., Solomon S.D., Vaduganathan M. Angioedema in COVID-19 // Eur Heart J. 2020. Vol. 41, N 34. P. 3283–3284. doi: 10.1093/eurheartj/ehaa452
21. Kuzemczak M., Kavvouras C., Alkhalil M., Osten M. ACE inhibitor-related angioedema in a COVID-19 patient-a plausible contribution of the viral infection? [letter] // Eur J Clin Pharmacol. 2021. doi: 10.1007/s00228-020-03082-w
22. Naranjo C.A., Busto U., Sellers E.M., et al. A method for estimating the probability of adverse drug reactions // Clin Pharmacol Ther. 1981. Vol. 30, N 2. P. 239–245. doi: 10.1038/clpt.1981.154
23. Pfaue A., Schuler P.J., Mayer B., et al. Clinical features of angioedema induced by renin-angiotensin-aldosterone system inhibition: a retrospective analysis of 84 patients // J Community Hosp Intern Med Perspect. 2019. Vol. 9, N 6. P. 453–459. doi: 10.1080/20009666.2019.1698259
24. Mihaela L.P., Florin A.V., Bocsan C., et al. Acquired angioedema induced by angiotensin-converting enzyme inhibitors — experience of a hospital-based allergy center // Exp Ther Med. 2020. Vol. 20, N 1. P. 68–72. doi: 10.3892/etm.2020.8474
25. Balla Z., Zsilinszky Z., Pólai Z., et al. The importance of complement testing in acquired angioedema related to angiotensin-converting enzyme inhibitors // J Allergy Clin Immunol Pract. 2021. Vol. 9, N 2. P. 947–955. doi: 10.1016/j.jaip.2020.08.052
26. Гурьянова И.Е., Жаранкова Ю.С., Полякова Е.А., и др. Молекулярно-генетическая диагностика врожденного ангионевротического отека // Весці Нацыянальнай акадэміі навук Беларусі. Серыя медыцынскіх навук. 2021. Т. 18, № 1. С. 25–35. doi: 10.29235/1814-6023-2021-18-1-25-35
27. Bas M., Hoffmann T.K., Bier H., Kojda G. Increased C-reactive protein in ACE-inhibitor-induced angioedema // Br J Clin Pharmacol. 2005. Vol. 59, N 2. P. 233–238. doi: 10.1111/j.1365-2125.2004.02268.x
28. Guzik T.J., Mohiddin S.A., Dimarco A., et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options // Cardiovasc Res. 2020. Vol. 116, N 10. P. 1666–1687. doi: 10.1093/cvr/cvaa106
29. Hassan K. Urticaria and angioedema as a prodromal cutaneous manifestation of SARS-CoV-2 (COVID-19) infection // BMJ Case Rep. 2020. Vol. 13, N 7. P. e236981. doi: 10.1136/bcr-2020-236981

AUTHORS' INFO

Corresponding author:
Tatiiana M. Sabalenka, MD, Cand. Sci. (Med.), Associate Professor; address: 210009, Frunze av., 27, Vitebsk, Republic of Belarus;
ORCID: http://orcid.org/0000-0002-8702-6486;
eLibrary SPIN: 9309-5550; e-mail: t.sobolen@tut.by

Co-authors:
Volha V. Zakharava, MD;
ORCID: http://orcid.org/0000-0002-6696-0704;
eLibrary SPIN: 8993-3484; e-mail: zakharovkan@mail.ru

Natallia R. Prakoshyna, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0002-3471-6977;
eLibrary SPIN: 4022-5469; e-mail: drnataliprr@gmail.com

ОБ АВТОРАХ

Автор, ответственный за переписку:
Соболенко Татьяна Михайловна, к.м.н., доцент;
адрес: Республика Беларусь, 210009, Витебск, пр-т Фрунзе, д. 27;
ORCID: http://orcid.org/0000-0002-8702-6486;
eLibrary SPIN: 9309-5550; e-mail: t.sobolen@tut.by

Соавторы:
Захарова Ольга Вячеславовна;
ORCID: http://orcid.org/0000-0002-6696-0704;
eLibrary SPIN: 8993-3484; e-mail: zakharovkan@mail.ru

Прокошина Наталья Робертовна, к.м.н.;
ORCID: https://orcid.org/0000-0002-3471-6977;
eLibrary SPIN: 4022-5469; e-mail: drnataliprr@gmail.com

DOI: https://doi.org/10.36691/RJA1436

Drug intolerance: age-related aspects

M.A. Grakhova[1], O.A. Rychkova[2], A.V. Braun[3], A.S. Sagitova[2], M.A. Nesterova[4]

[1] Regional Clinical Hospital No 1, Tyumen, Russian Federation
[2] Tyumen State Medical University, Tyumen, Russian Federation
[3] INVITRO-Ural LLC, Tyumen, Russian Federation
[4] Tyumen Region Infection Pathology Research Institute, Tyumen, Russian Federation

ABSTRACT

BACKGROUND: Drug hypersensitivity is an adverse reaction caused by immune or non-immune mechanisms to the intake of adequate doses of drugs. To avoid a dangerous situation, correctly collected pharmacological history, taking into account all the characteristics of the patient (gender, age, concomitant pathology), and knowledge of the mechanism of action of drugs can help a practicing physician who does not currently have a reliable method for diagnosing drug hypersensitivity.

AIM: Identification of age-specific drug intolerance.

MATERIALS AND METHODS: The study was conducted from 2017 to 2020 and included 200 outpatient medical history forms of individuals diagnosed with an unspecified pathological reaction to a drug or medication. All drug reactions were based on patient's own statements and were allocated as dichotomous variables. The results were analyzed by non-parametric statistics (Pearson's chi-square).

RESULTS: Three groups of patients were identified: 18–44 years (n=49), 45–60 years (n=60), ⩾61 (n=91). The odds of incomprehensible reactions were 2.2 times higher in patients in group 3 than in patients in the other groups. Group 3 patients were 12 times more likely to have an itchy reaction to medications than patients in the other groups. Group 1 patients were 3 times more likely to have urticaria than patients in groups 2 and 3. The odds of drug intolerance to angiotensin-converting enzyme (ACE) inhibitors were 2.6 times higher in patients in group 3 than in patients in the other groups. When comparing clinical manifestations of drug intolerance to penicillin and cephalosporin antibiotics, no significant differences were found in all patients. The presence of allergies and somatic pathology of ⩾3 systems did not significantly affect the possibility of reactions of varying severity to ⩾3 drugs in these groups.

CONCLUSIONS: Patient's age has no effect on the possibility of reactions to certain groups of drugs. The exception was ACE inhibitors, which is most likely due to the higher frequency of prescribing antihypertensive therapy in patients in this age group. The aggravation of clinical manifestations and the occurrence of polypharmacy are not associated with age and comorbid background. Age and non-life-threatening clinical manifestations of drug intolerance were correlated, which indicates the absence of the reliable effect of age on the possibility of anaphylactic shock or angioedema.

Keywords: drug intolerance; drug allergy; drug hypersensitivity; age

For citation: Grakhova MA, Rychkova OA, Braun AV, Sagitova AS, Nesterova MA. Drug intolerance: age-related aspects. *Russian Journal of Allergy*. 2021;18(3):16–34. DOI: https://doi.org/10.36691/RJA1436

Возрастные аспекты реакций на лекарственные препараты

М.А. Грахова[1], О.А. Рычкова[2], А.В. Браун[3], А.С. Сагитова[2], М.А. Нестерова[4]

[1] Областная клиническая больница № 1, Тюмень, Российская Федерация
[2] Тюменский государственный медицинский университет, Тюмень, Российская Федерация
[3] ООО «ИНВИТРО-Урал», Тюмень, Российская Федерация
[4] Тюменский научно-исследовательский институт краевой инфекционной патологии, Тюмень, Российская Федерация

АННОТАЦИЯ

ОБОСНОВАНИЕ. Лекарственная гиперчувствительность представляет собой обусловленные иммунными или неиммунными механизмами нежелательные реакции на приём адекватных доз лекарственных препаратов. Практикующему врачу, не имеющему на сегодняшний день достоверного метода диагностики лекарственной гиперчувствительности, поможет избежать опасной ситуации только правильно собранный фармакологический анамнез с учётом всех характеристик пациента (пол, возраст, сопутствующая патология) и знание механизма действия лекарственных средств.

ЦЕЛЬ — выявить возрастные особенности реакций на лекарственные препараты.
МАТЕРИАЛ И МЕТОДЫ. Исследование проводилось в период с 2017 по 2020 г. В исследование включены 200 амбулаторных карт пациентов с диагнозом «Патологическая реакция на лекарственное средство или медикаменты, неуточнённая». Данные фармако-аллергологического анамнеза указывались только на основании информации, полученной от пациента и, возможно, ранее выставленного в другом ЛПУ диагноза лекарственной гиперчувствительности. Все реакции на лекарственные препараты были распределены по дихотомическим переменным. Результаты исследований проанализированы методом непараметрической статистики (хи-квадрат Пирсона).
РЕЗУЛЬТАТЫ. Выделены 3 группы пациентов: 18–44 года (n=49); 45–60 лет (n=60); 61 год и старше (n=91). У пациентов 3-й группы вероятность появления зуда и не обусловленных гиперчувствительностью реакций на лекарственные препараты выше, чем у других, в 12 и 2,2 раза соответственно. Пациенты 1-й группы в 3 раза чаще подвержены развитию крапивницы, чем участники групп 2 и 3, а вероятность реакций на ингибиторы ангиотензинпревращающего фермента выше в 2,6 раза у пациентов 3-й группы. При сравнении клинических проявлений лекарственной гиперчувствительности на антибиотики пенициллинового и цефалоспоринового ряда достоверных различий между пациентами не выявлено. Наличие аллергии и соматической патологии трёх и более систем у пациентов наблюдаемых групп достоверно не повлияло на возможность возникновения реакций разной степени тяжести при приёме ⩾3 препаратов одновременно.
ЗАКЛЮЧЕНИЕ. Возраст пациента не оказывает влияния на вероятность возникновения реакций на определённые группы препаратов (исключением стали ингибиторы ангиотензинпревращающего фермента, что, скорей всего, обусловлено более высокой частотой назначения антигипертензивной терапии у пациентов данной возрастной группы). С возрастом и коморбидным фоном не связаны ни усугубление клинических проявлений, ни возникновение полипрагмазии. Выявленная корреляционная зависимость между возрастом и не угрожающими жизни клиническими проявлениями реакций на лекарственные препараты свидетельствует об отсутствии достоверного влияния возраста на возможность возникновения анафилактического шока или ангионевротического отёка.

Ключевые слова: реакции на лекарственные препараты; лекарственная аллергия; лекарственная гиперчувствительность; возраст

Для цитирования: Грахова М.А., Рычкова О.А., Браун А.В., Сагитова А.С., Нестерова М.А. Возрастные аспекты реакций на лекарственные препараты // *Российский аллергологический журнал*. 2021. Т. 18. № 3. С. 16–34. DOI: https://doi.org/10.36691/RJA1436

Статья поступила 25.03.2021 Принята к печати 08.09.2021 Опубликована 20.09.2021
Received: 25.03.2021 Accepted: 08.09.2021 Published: 20.09.2021

Background

Drug-induced hypersensitivity remains an urgent problem in practical health care due to the risk of severe allergic reactions, which often require hospitalization or long-term treatment [1].

In clinical practice, adverse drug reactions occur in 0.04–3.1% of patients. One in 4,000 patients who visits the emergency department is admitted with a life-threatening condition after medication intake [2].

There are two types of adverse drug reactions, namely those related (type A, predictable reactions) and unrelated (type B, unpredictable reactions) with the pharmacological action of the drug [3–5]. Predictable reactions are more common and are related to dose, pharmacological effect, and cross-reactions between concurrently administered drugs. Unpredictable reactions are less common (20–25% of patients) and are due to the individual characteristics of the patient. This type of reaction includes non-allergic congenital hypersensitivity (idiosyncrasy) and drug-induced hypersensitivity (allergic and non-allergic).

Drug-induced hypersensitivity represents adverse reactions to the intake of adequate doses of drugs caused by immune (drug allergy) or non-immune (non-allergic drug hypersensitivity) mechanisms [6, 7]. Given the lack of a reliable method for diagnosing drug-induced hypersensitivity nowadays [8–10], it must be admitted that only a correctly collected pharmacological history, including all patient characteristics (gender, age, concomitant pathology) and awareness of the mechanism of drug action, will help the practicing physician to avoid a hazardous situation. [11].

Currently, the risk factors that contribute to the development and aggravation of the course of drug-induced hypersensitivity include genetic predisposition, demographic characteristics, and comorbid conditions. Among the demographic risk factors, which include female gender, race, and old age, only the latter, according to several authors, is the most unfavorable and is associ-

ated with the severity and prevalence of drug-induced hypersensitivity cases [12–15].

This work aimed to identify age-related characteristics of drug-induced reactions.

Materials and methods

Study design

An observational single-center cohort uncontrolled retrospective study was performed. The study design diagram is presented in Fig. 1.

Inclusion criteria

The criterion for inclusion of patients in the study was reactions to one or more drugs with a diagnosis of unspecified pathological reaction to a drug or drugs.

Conditions of conducting

In the Regional Clinical Hospital No. 1 (Tyumen) of the Tyumen region, 200 outpatient patient records were selected and analyzed.

Study duration

The study was performed for three years (2017 to 2020).

Description of the medical intervention

Out of 3650 primary outpatient records of patients, the outpatient records of 200 patients (171 women and 29 men) with a diagnosis T88.7 (unspecified pathological reaction to a drug or drugs) according to ICD-10 were included in the study and analyzed.

The anamnesis data of 200 patients were entered into a table with the columns indicating full name, age, gender, place of residence, the name of the drug which induced the reaction, clinical manifestations of drug-induced hypersensitivity, namely urticaria, angioneurotic edema, cough, choking, dermatitis, anaphylactic shock; other manifestations of drug-induced hypersensitivity such as dizziness, tinnitus, headache, tachycardia, deterioration in the condition, dyspeptic disorders; somatic pathology in the ENT organs, respiratory (chronic obstructive pulmonary

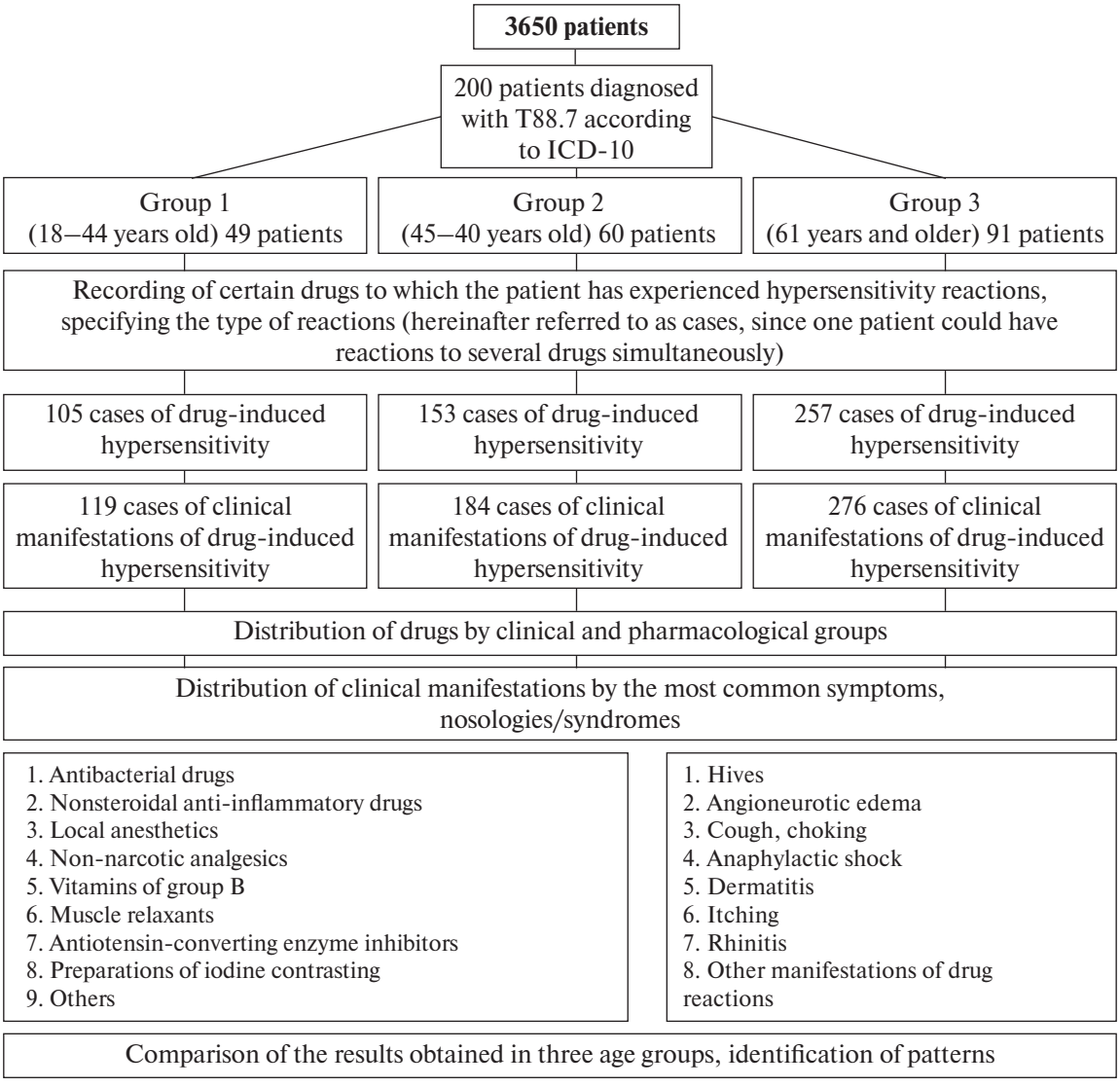

Fig. 1. Study design diagram.

disease), cardiovascular, digestive, genitourinary, nervous, and endocrine systems; helminthiases, hematological, oncological, autoimmune diseases; allergopathology including allergic rhinitis, urticaria, angioneurotic edema, bronchial asthma (sensitization and eosinophilia were indicated separately). In addition, all columns except full name, age, place of residence, the name of the drug which induced the reaction, eosinophilia, and helminthiasis were filled with dichotomous variables (presence of a disease/reaction — 1; no disease/reaction — 0).

Main study outcome

The aspects of drug-induced hypersensitivity were revealed in patients of different age groups, namely in young patients (18–44 years old), middle-aged patients (45–60 years old), elderly and senile patients (61 years and older).

Additional study outcomes

The most common groups of drugs causing adverse reactions and the range of these reactions were identified in patients of different age groups, namely in young patients (18–44 years old), middle-aged patients (45–60 years old), elderly and senile patients (61 years and older).

Subgroup analysis

Three age groups of patients were formed according to the criteria of the World Health Organization, namely 18–44 years implied young age (n = 49); 45–60 years indicated middle-aged patients (n = 60); 61 years and older corresponded to elderly and senile patients (n = 91). Age was indicated at the time of the patient's visit.

Outcome registration methods

All reactions to drugs and the presence of comorbidities were recorded according to the information provided by the patients and distributed according to dichotomous variables (the presence of a disease/reaction — 1; no disease/reaction — 0). Each episode of reaction to one drug that occurred within one year after the patient's visit was taken as a unit and considered a case (a total of 515 cases were identified). The distribution of drugs into groups was performed according to the clinical and pharmacological characteristics. The groups were formed provided that the drug was indicated three times or more (except for drugs for anesthesia ketamine and midazolam). All other drugs were assigned to the "Others" group. We have identified 33 groups of drugs.

The distribution of drugs by groups and subgroups is presented in Table 1.

Ethical considerations

Conclusion of the protocol of the Ethics Committee at the Tyumen State Medical University No. 100 dated 06/11/2021 indicated that "Based on the analysis of the documentation submitted, the Ethics Committee at the Tyumen State Medical University decided that, given the non-interventional nature of the study, this study does not require ethical examination."

Statistical analysis

Principles for calculating the sample size. The sample size was not pre-calculated.

Methods of statistical data analysis included Microsoft Excel (Microsoft, USA) and STATISTICA 6.0 (StatSoft Russia, Russia) software for data processing. We analyzed the results of the studies using the methods of nonparametric statistics. Descriptive statistics were performed by estimating the arithmetic mean (M) and mean-square deviation ($M \pm s$). To assess intergroup differences, given categorical data, calculations were made using four-field tables. The rows represented the factor values (age ranges) and the columns represented the outcome values. Depending on the smallest value of the expected event (out of four), the analysis method was chosen as follows. If the smallest value of the expected event was less than 5, Fisher's exact test was used for comparison; if the smallest value of the expected event was within the range from 5 to 10, Yates continuity-corrected Pearson's chi-square test was used for comparison; if the smallest value of the expected event was more than 10, the Pearson chi-square test was chosen. To quantify the dependence of the probability of an outcome on the presence of a factor, the odds ratio was calculated with a 95% confidence interval (CI). The critical significance level of the null statistical hypothesis p (the absence of differences and influences) was taken equal to 0.05.

Results

Objects (participants) of the study

The study analyzed 200 outpatient records of patients (171 women and 29 men) whose average age was 55 ± 15 years (range: 18–85 years).

Clinical and demographic characteristics of patients are presented in Table 2.

Key research outcomes

Clinical manifestations of adverse drug reactions

The distribution of clinical drug-induced manifestations in each age group did not differ significantly. However, reactions in the form of angioneurotic edema and dermatitis were among the three most common reactions in each group, namely 27.73% and 14.29% in group 1; 22.28% and 21.74% in group 2; and 19.57% and 21.38% in group 3, respectively.

In group 1, along with angioneurotic edema, there were reactions in the form of urticaria (27.73%), in the p 2, there were coughing and choking (15.76%), and in group 3, other manifestations of drug-induced reactions prevailed (22.83%); Table 3.

Comparison of clinical manifestations of drug-induced reactions in patients of three age groups demonstrated significant differences in the number of reactions (Fig. 2).

Other manifestations of adverse drug reactions (dizziness, tinnitus, headache, tachycardia, deterioration

DOI: https://doi.org/10.36691/RJA1436

Table 1. Drugs for which hypersensitivity have been reported

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
1	Non-narcotic analgesics		Acetylsalicylic acid + paracetamol (Citramon)	4 (0.78)	18.18
			Metamizole sodium	13 (2.52)	59.09
			Paracetamol	5 (0.97)	22.73
2	Opioid analgesics		Tramadol	1 (0.19)	25.00
			Fentanyl	3 (0.58)	75.00
3	Angiotensin 2 receptor antagonists	AT2 inhibitors	Valsartan	1 (0.19)	33.33
		AT2 inhibitors	Losartan	2 (0.39)	66.67
4	Antimicrobial drugs	Aminoglycosides	Streptomycin	2 (0.39)	100.00
		Amphenicols	Chloramphenicol	5 (0.97)	100.00
		Ansamycins	Rifaximin	1 (0.19)	100.00
		Macrolides	Azithromycin	1 (0.19)	14.29
			Clarithromycin	3 (0.58)	42.86
			Erythromycin	3 (0.58)	42.86
		Unspecified	Unspecified	1 (0.19)	100.00
		Nitrofurans	Nifurantel	1 (0.19)	50.00
			Furazidin	1 (0.19)	50.00
		Penicillins	Amoxicillin	11 (2.13)	22.92
			Ampicillin	2 (0.39)	4.17
			Amoxiclav	1 (0.19)	2.08
			Unspecified	34 (6.59)	70.83
		Tetracyclines	Doxycycline	4 (0.78)	66.67
			Tetracycline	2 (0.39)	33.33
		Fluoroquinolones	Levofloxacin	2 (0.39)	2.02
			Ciprofloxacin	5 (0.97)	5.05
		Cephalosporins	Cefazolin	2 (0.39)	10.00
			Cefexime	2 (0.39)	10.00
			Cefotaxime	4 (0.78)	20.00
			Ceftazidime	1 (0.19)	5.00
			Ceftriaxone	6 (1.16)	30.00
			Unspecified	5 (0.97)	25.00

DOI: https://doi.org/10.36691/RJA1436

Table 1. Continuation

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
5	Antibacterial sulphanilamide drugs		Co-trimoxazole	3 (0.58)	75.00
			Sulfanilamide	1 (0.19)	25.00
6	Antihypertensive drugs	Central vasodilators	Moxonidine	3 (0.58)	75.00
		Peripheral vasodilators	Reserpine	1 (0.19)	25.00
7	Antihistamines		Desloratadine	1 (0.19)	6.25
			Diphenhydramine	9 (1.74)	56.25
			Loratadine	1 (0.19)	6.25
			Fenspiride	1 (0.19)	6.25
			Chloropyramine	3 (0.58)	18.75
			Cetirizine	1 (0.19)	6.25
8	Antioxidants		Ab to S100 protein. Ab to endothelium NO-synthase	1 (0.19)	14.29
			Ethylmethylhydroxypyridine succinate	6 (1.16)	85.71
9	Antiseptics		Potassium permanganate	1 (0.19)	25.00
			Strepsils (amylmetacresol + dichlorobenzyl alcohol)	1 (0.19)	25.00
			Chlorhexidine bigluconate	1 (0.19)	25.00
			Ethanol	1 (0.19)	25.00
10	Ca-channel blockers		Lecarnidipine	2 (0.39)	33.33
			Nifedipine	4 (0.78)	66.67
11	Broncholytic drug. phosphodiesterase inhibitor		Aminophylline	8 (1.55)	100.00
12	β_1-adrenergic receptor blockers		Bisoprolol	2 (0.39)	66.67
			Metoprolol	1 (0.19)	33.33
13	Venotonic		Diosmin	1 (0.19)	33.33
			Troxerutin	1 (0.19)	33.33
			Thiamine + escin	1 (0.19)	33.33
14	B vitamins		Group B vitamins	41 (7.95)	100.00

DOI: https://doi.org/10.36691/RJA1436

Table 1. Continuation

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
15	GCS		Dexamethasone	2 (0.39)	28.57
			Prednisone	4 (0.78)	57.14
			Triamcinolone	1 (0.19)	14.29
16	ACE inhibitors		Captopril	3 (0.58)	14.29
			Lisinopril	3 (0.58)	14.29
			Perindopril	6 (1.16)	28.57
			Enalapril	8 (1.55)	38.10
			Unspecified	1 (0.19)	4.76
17	Macro and trace elements		Calcium gluconate	1 (0.19)	7.69
			Calcium chloride	5 (0.97)	38.46
			Calcium + Vitamin D	1 (0.19)	7.69
			Magnesium sulfate	4 (0.78)	30.77
			Multivitamins	1 (0.19)	7.69
			Ferrum Lek	1 (0.19)	7.69
18	Local anesthetics	Paraaminogroup	Lidocaine	30 (5.81)	49.18
		Amides	Novocaine	31 (6.01)	50.82
19	Metabolic drugs		Inosine	5 (0.97)	62.50
			Mildronate	3 (0.58)	37.50
20	Muscle relaxants		Baclofen	1 (0.19)	8.33
			Rocuronium	2 (0.39)	16.67
			Suxamethonium chloride	1 (0.19)	8.33
			Tizanidine	3 (0.58)	25.00
			Tolperisone	5 (0.97)	41.67
21	Myotropic antispasmodics		Dibasol	1 (0.19)	25.00
			Drotaverine	1 (0.19)	25.00
			Mebeverine	1 (0.19)	25.00
			Papaverine	1 (0.19)	25.00
22	Nootropic drugs		Aminophenyl-butyric acid	1 (0.19)	80.00
			Piracetam	4 (0.78)	20.00

DOI: https://doi.org/10.36691/RJA1436

Table 1. Continuation

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
23	NSAID	Comb. NSAIDs	Dexketoprofen	1 (0.19)	50.00
			Paracetamol + Ibuprofen	1 (0.19)	50.00
		Topical NSAIDs	Benzidiamine hydrochloride	1 (0.19)	100.00
		NSAIDs (mainly COX-2 selective)	Meloxicam	7 (1.36)	46.67
			Nimesulide	7 (1.36)	46.67
			Etoricoxib	1 (0.19)	6.67
		NSAIDs (COX-1. 2 non-selective)	Aceclofenac	2 (0.39)	5.56
			Acetylsalicylic acid	13 (2.52)	36.11
			Diclofenac	10 (1.94)	27.78
			Ibuprofen	3 (0.58)	8.33
			Ketoprofen	3 (0.58)	8.33
			Ketorolac	3 (0.58)	8.34
			Lornoxicam	1 (0.19)	2.78
			Tenoxicam	1 (0.19)	2.78
		Unspecified	Unspecified	4 (0.78)	100.00
24	Plasma-substituting agents		Rheopolyglucin	3 (0.58)	100.00
25	Cartilage tissue regeneration stimulating drug		Glucosamine + chondroitin	1 (0.19)	33.33
			Chondroitin	2 (0.39)	66.67
26	Intravenous anesthesia agents		Propofol	3 (0.58)	100.00
27	Non-inhalation anesthesia agents		Ketamine	1 (0.19)	100.00
28	Iodine-contrast agents		Radiopaque diagnostic agent for intravascular and intracavitary administration	23 (4.45)	100.00
29	Anti-inflammatory drugs used to treat NUC and Crohn's disease		Sulphasalazine	3 (0.58)	100.00

DOI: https://doi.org/10.36691/RJA1436

Table 1. Ending

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
30	Microcirculation improving drugs		Betahistine	1 (0.19)	25.00
			Pentoxifylline	3 (0.58)	75.00
31	Antiviral drugs	HIV treatment drugs	Raltegravir	1 (0.19)	50.00
			Etravirine	1 (0.19)	50.00
		Antiviral/antihistamine drugs	Abs to human interferon-gamma. Abs to histamine. Abs to CD4	1 (0.19)	16.67
		Antiviral drugs	Dioxotetrahydrooxytetrahydro-naphthaline	1 (0.19)	16.67
		Antiviral drugs	Pentandioic acid imidazolyl ethanamide	1 (0.19)	16.67
		Antiviral drugs/interferon inducers	Meglumine acridone acetate	1 (0.19)	16.67
		Antiviral drugs	Rimantadine	1 (0.19)	16.67
		Antiviral drugs/interferon inducers	Tilorone	1 (0.19)	16.67
32	Dormitive and sedative drugs for premedication and anesthetic induction		Midazolam	1 (0.19)	100.00
33	Animal origin agents		Aprotinin	1 (0.19)	9.09
			Bioactive sea fish concentrate	1 (0.19)	9.09
			Deproteinized calf blood hemoderivative	4 (0.78)	36.36
			Lanolin cream	1 (0.19)	9.09
			Pig brain peptides	3 (0.58)	27.27
			Tetanus toxoid	1 (0.19)	9.09
34	Other			43 (8.33)	8.33

Note. Ab — antibodies; GCS — glucocorticoid steroids; ACE inhibitors — angiotensin-converting enzyme inhibitors; NSAIDs — nonsteroidal anti-inflammatory drugs; COX-2 — cyclooxygenase-2; NUC — nonspecific ulcerative colitis; HIV — human immunodeficiency virus.

Table 2. Clinical and demographic characteristics of patients

Indicator	All subjects	Group 1 18–44 years *n* = 49	Group 2 45–60 years *n* = 60	Group 3 61 years and older *n* = 91
Men. *n* (%)	29 (14.5)	11 (22.45)	8 (13.33)	10 (10.99)
Women. *n* (%)	171 (85.5)	38 (77.55)	52 (86.67)	81 (89.01)
Somatic pathology. *n* (%)	**183 (91.5)**	**40 (81.63)**	**56 (93.33)**	**87 (95.6)**
CVS pathology. *n* (%)	100 (54.64)	4 (10)	32 (53.33)	64 (70.33)
UGS pathology. *n* (%)	67 (36.61)	12 (30)	22 (36.67)	33 (36.26)
GIT pathology. *n* (%)	62 (33.88)	12 (30)	23 (38.33)	27 (29.67)
Endocrine pathology. *n* (%)	56 (30.60)	7 (17.5)	20 (33.33)	29 (31.87)
Pathology of the hepatobiliary system. *n* (%)	43 (23.50)	8 (20)	11 (18.33)	24 (26.37)
Respiratory system pathology (COPD. BOS). *n* (%)	31 (16.94)	3 (7.5)	8 (13.33)	20 (21.98)
NS pathology. *n* (%)	30 (16.39)	8 (20)	9 (15)	13 (14.29)
Helminthiasis. *n* (%)	30 (16.39)	10 (25)	7 (11.67)	12 (13.19)
ENT pathology. *n* (%)	20 (10.93)	9 (22.5)	6 (10)	7 (7.69)
US pathology. *n* (%)	17 (9.29)	4 (10)	5 (8.33)	8 (8.79)
Oncology. *n* (%)	11 (6.01)	1 (2.5)	2 (3.33)	8 (8.79)
Autoimmune diseases. *n* (%)	10 (5.46)	2 (5)	3 (5)	5 (5.49)
Blood pathology. *n* (%)	9 (4.92)	2 (5)	4 (6.67)	3 (3.3)
Allergic pathology. *n* (%)	**38 (19)**	**9 (18.37)**	**13 (21.67)**	**16 (17.58)**
Allergic rhinitis. *n* (%)	19 (50)	5 (55.56)	7 (53.85)	7 (43.75)
Dermatitis. *n* (%)	12 (31.58)	2 (22.22)	5 (38.46)	6 (37.5)
Urticaria. *n* (%)	6 (15.79)	1 (11.11)	1 (7.69)	4 (25)
Angioneurotic edema. *n* (%)	6 (15.79)	1 (11.11)	3 (23.08)	2 (12.5)
Bronchial asthma. *n* (%)	6 (15.79)	2 (22.22)	6 (46.15)	6 (37.5)

Note. CVS — cardiovascular system; UGS — urogenital system; GIT — gastrointestinal tract; COPD — chronic obstructive pulmonary disease; BOS — broncho-obstructive syndrome; NS — nervous system; US — urinary system.

Table 3. Clinical manifestations of drug hypersensitivity

Clinical manifestations of drug-induced hypersensitivity	All subjects	Group 1 18–44 years	Group 2 45–60 years	Group 3 61 years and older
Total number of cases of clinical manifestations, n.	579	119	184	276
Angioneurotic edema, *n* (%)	128 (22.11)	33 (27.73)	41 (22.28)	54 (19.57)
Dermatitis, *n* (%)	116 (20.03)	17 (14.29)	40 (21.74)	59 (21.38)
Other manifestations, *n* (%)	98 (16.93)	12 (10.08)	23 (12.50)	63 (22.83)**
Urticaria, *n* (%)	85 (14.68)	33 (27.73)*	25 (13.59)	27 (9.78)
Anaphylactic shock, *n* (%)	69 (11.92)	16 (13.45)	24 (13.04)	29 (10.51)
Cough and choking, *n* (%)	61 (10.54)	7 (5.88)	29 (15.76)	25 (9.06)
Itching, *n* (%)	12 (2.07)	0 (0)	1 (0.54)	11 (3.99)**
Rhinitis, *n* (%)	10 (1.73)	1 (0.84)	1 (0.54)	8 (2.90)

Note. * $p < 0.05$ if data of the 1st group were compared with two other groups; ** $p < 0.05$ if data of the 3rd group were compared with two other groups. The table does not include patients (17 people: groups 1 and 2 — for two people; group 3 — 13 people) with cough while taking an ACE inhibitor.

 DOI: https://doi.org/10.36691/RJA1436

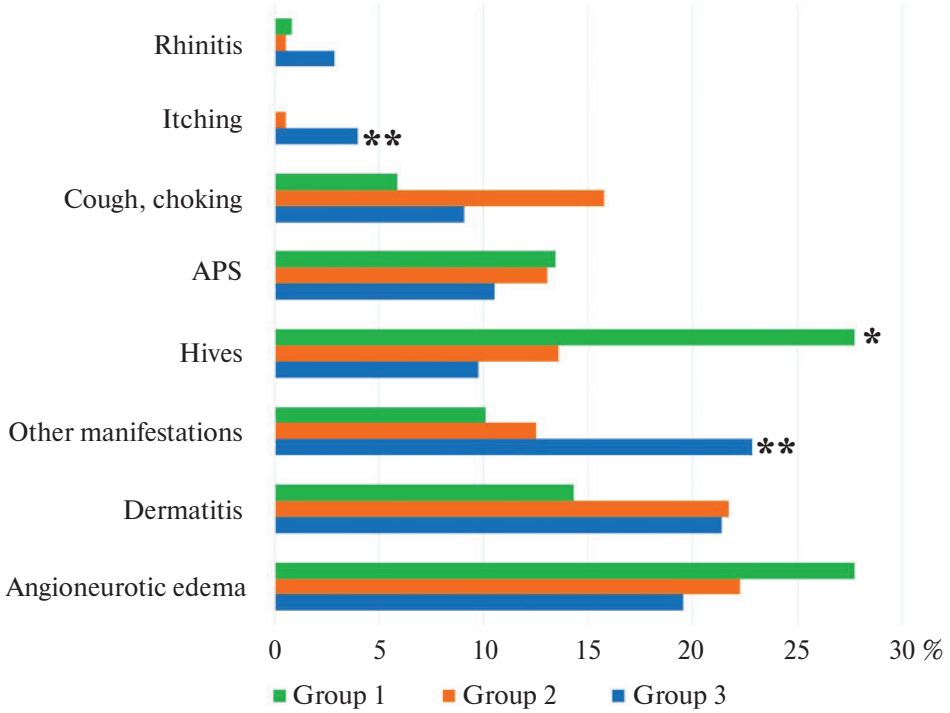

Fig. 2. Clinical manifestations of drug intolerance in all patients.

Note: * p <0.05 if data of the 1st group were compared with two other groups; ** p <0.05 if data of the 3rd group were compared with two other groups; АФШ — anaphylactic shock. This diagram did not include a cough response to ACE inhibitors.

of the condition, dyspeptic disorders) in elderly and senile patients were registered in 63 (22.83%) cases, while in other groups, these were in 35 cases (10.08% in the group 1 and 12.50% in the group 2). The differences in indicators assessed using Pearson's chi-square test were statistically significant (p = 0.001). The probability of other manifestations of drug-induced hypersensitivity in elderly and senile patients was 2.2 times more likely than in younger patients (95% CI 1.382–3.395).

Reactions in the form of drug-induced itching in elderly and senile patients were noted in 11 (3.99%) cases, while in patients of other ages, they were registered in one case (0.54% in group 2). The differences in indicators evaluated using Yates corrected Pearson's chi-square test was statistically significant (p = 0.007). Elderly and senile patients were 12 times more likely to develop drug-induced itching than younger patients (95% CI 1.553–94.391).

Drug-induced urticaria in young patients occurred in 33 (27.73%) cases and in 52 cases in patients of other ages (13.59% in group 2 and 9.78% in group 3). The differences in indicators assessed using Pearson's chi-square test were statistically significant (p < 0.001). The probability of urticaria in young patients was three times higher than in older patients (95% CI 1.863–4.994).

Drugs

The incidence of adverse reactions to different groups of drugs in three age groups did not differ significantly from the data of the entire sample (Fig. 3).

In group 1, 105 cases of reactions to drugs were detected, as well as 153 and 257 cases in group 2 and group 3, respectively.

In three groups, in terms of incidence of drug-induced reactions, antibiotics ranked first (20% in group 1; 19.61% in group 2; 18.68% in group 3), while nonsteroidal anti-inflammatory drugs (12.38% in group 1; 12.42% in group 2; 9.73% in group 3) and local anesthetics (11.43% in group 1; 14.38% in group 2; 10.51% in group 3) ranked second and third.

Group B vitamins ranked fourth in incidence in groups 2 and 3 (8.5% and 8.17%) and were superseded by non-narcotic analgesics (10.48%) in group 1. In groups 2 and 3, reactions to non-narcotic analgesics were less common in 1.96% and 3.5% of patients, respectively.

In the group 2, muscle relaxants ranked fifth in the incidence (5.23%). In group 3, these were angiotensin-converting enzyme inhibitors (ACE inhibitors) (5.84%), the reactions which were less common in groups 1 and 3, namely 0.95% and 2.61%, respectively.

Reactions to iodine-contrast drugs were registered with approximately equal frequency in all groups (0.95% in group 1; 1.96% in group 2; and 3.5% in group 3; Table 4).

When comparing the incidence of reactions to different groups of drugs in patients of three age groups, significant differences were revealed only in the category of ACE inhibitors in elderly and senile patients. Adverse reactions to ACE inhibitors in elderly and senile patients were noted in 15 (6%) cases, while in patients of other

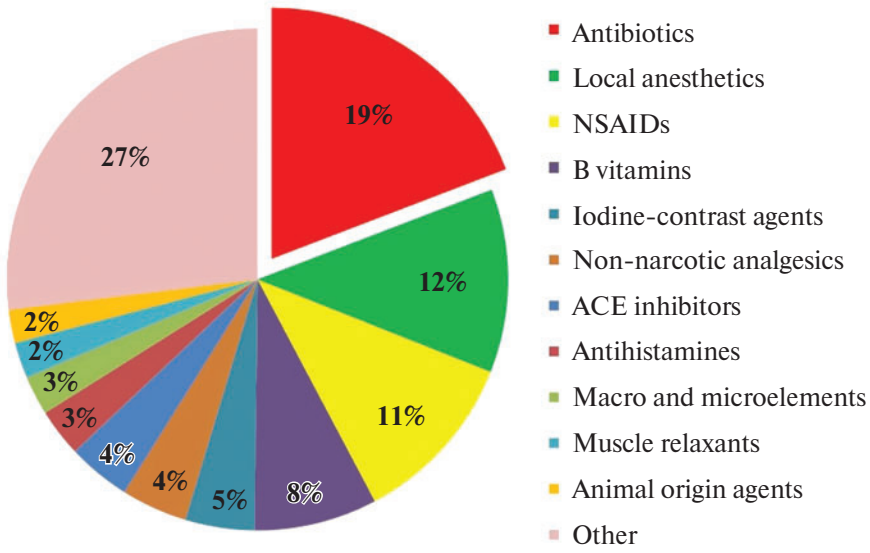

Fig. 3. Structure of the most frequently encountered groups of drugs in the whole sample, which caused hypersensitivity reactions
Note. НПВС — non-steroidal anti-inflammatory drugs; иАПФ — angiotensin converting enzyme inhibitors.

ages, they were recorded in 6 (2.3%) cases. The differences in indicators assessed using Pearson's chi-square test were statistically significant ($p = 0.044$). The probability of reactions to ACE inhibitors in elderly and senile patients was 2.6 times higher than in younger patients (95% CI 0.998–6.847).

Antibacterial drugs

Among antibiotics, in terms of incidence of drug-induced hypersensitivity reactions in all age groups, the leading positions were taken by drugs of the penicillin series (42.86% in the group 1; 50% in the group 2; 50% of the subjects in the group 3) and cephalosporins (28.57% in the group 1, 26.67% in the group 2, and 12.5% of patients in the group 3) (Fig. 4; Table 4). A similar distribution of antibiotic groups is noted in patients from the general sample (48.48% of penicillins and 20.2% of cephalosporins).

When comparing the clinical manifestations of drug-induced hypersensitivity to the penicillin and cephalosporin series antibiotics, no significant differences were revealed in patients of all age groups.

Angiotensin-converting enzyme inhibitors

For the entire sample, the incidence of adverse reactions to ACE inhibitors was 4.07% (Table 5), most of which (5.84%) were significantly detected in patients of age 3.

When comparing the clinical manifestations of reactions to ACE inhibitors in patients of all groups, no significant differences were found (Fig. 5), and 68% of all reactions to this group of drugs were represented by cough (side effect of ACE inhibitors). Angioneurotic edema was registered in three patients of group 2 (75%). Such reactions as urticaria, dermatitis, and anaphylactic shock have not been recorded.

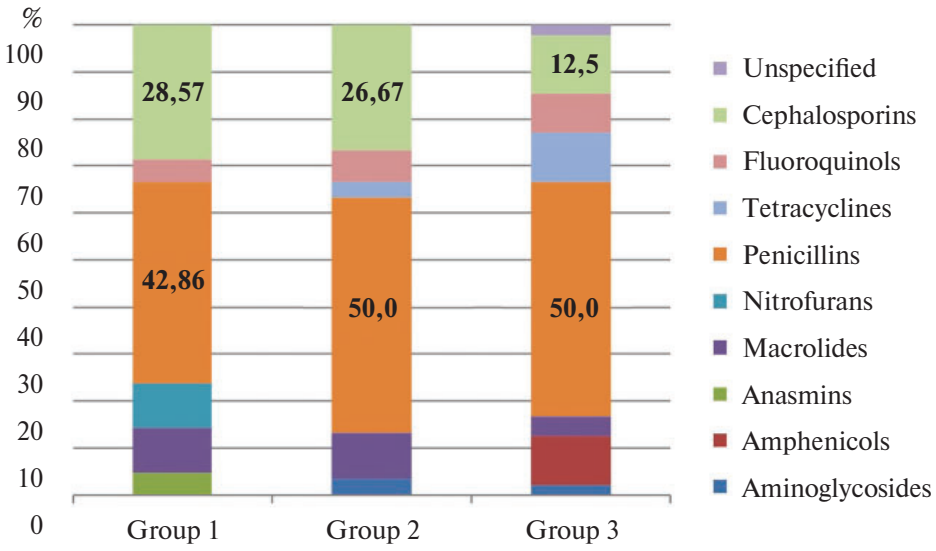

Fig. 4. Structure of clinical manifestations of drug intolerance to angiotensin-converting enzyme inhibitors in all groups.

 DOI: https://doi.org/10.36691/RJA1436

Table 4. Groups of drugs, which caused the most frequent drug hypersensitivity reactions in three age groups

Clinical and pharmacological group of the drugs	Incidence of drug intolerance reactions		
	Group 1 *n* = 105	Group 2 *n* = 153	Group 3 *n* = 257
Antibacterial drugs, *n* (%)	**21 (20)**	**30 (19.61)**	**48 (18.68)**
Aminoglycosides, *n*	0	1	1
Amphenicols, *n*	0	0	5
Anasmins, *n*	1	0	0
Macrolides, *n*	2	3	2
Nitrofurans, *n*	2	0	0
Penicillins, *n*	9	15	24
Tetracyclines, *n*	0	1	5
Fluoroquinolones, *n*	1	2	4
Cephalosporins, *n*	6	8	6
Unspecified, *n*	0	0	1
NSAIDs, *n* (%)	**13 (12.38)**	**19 (12.42)**	**26 (10.12)**
Combined NSAIDs, *n*	1	0	0
Local NSAIDs, *n*	0	0	1
NSAIDs (mainly COX-2/selective), *n*	2	7	6
NSAIDs (COX-1, 2 non-selective), *n*	10	10	17
Unspecified, *n*	0	2	2
Local anesthetics, *n* (%)	**12 (11.43)**	**22 (14.38)**	**27 (10.51)**
Amides, *n*	9	11	10
Paraamino group, *n*	3	11	17
Non-narcotic analgesics, *n* (%)	**11 (10.48)**	**3 (1.96)**	**8 (3.11)**
Combined with paracetamol, *n* (% of the group)	7	0	0
Metamizole sodium, *n*	4	2	7
Paracetamol, *n*	0	1	1
B vitamins, *n* (%)	**7 (6.67)**	**13 (8.5)**	**21 (8.17)**
Muscle relaxants, *n* (%)	**1 (0.95)**	**8 (5.23)**	**3 (1.17)**
Baclofen, *n*	0	0	1
Rocuronium, *n*	0	2	0
Suxamethonium chloride, *n*	0	1	0
Tizanidine, *n*	0	2	1
Tolperisone, *n*	1	3	1
ACE inhibitors, *n* (%)	**1 (0.95)**	**4 (2.61)**	**15 (5.84)**
Captopril, *n*	0	1	2
Lisinopril, *n*	0	0	3
Perindopril, *n*	1	2	3
Enalapril, *n*	1	0	7
Unspecified, *n*	0	1	0
Iodine-contrast agents, *n* (%)	**6 (5.72)**	**8 (5.23)**	**9 (3.5)**
Others, *n* (%)	**33 (31.42)**	**46 (30.06)**	**100 (38.9)**

Note. NSAIDs — Nonsteroidal anti-inflammatory drugs; COX — cyclooxygenase; ACE inhibitors — angiotensin-converting enzyme inhibitors.

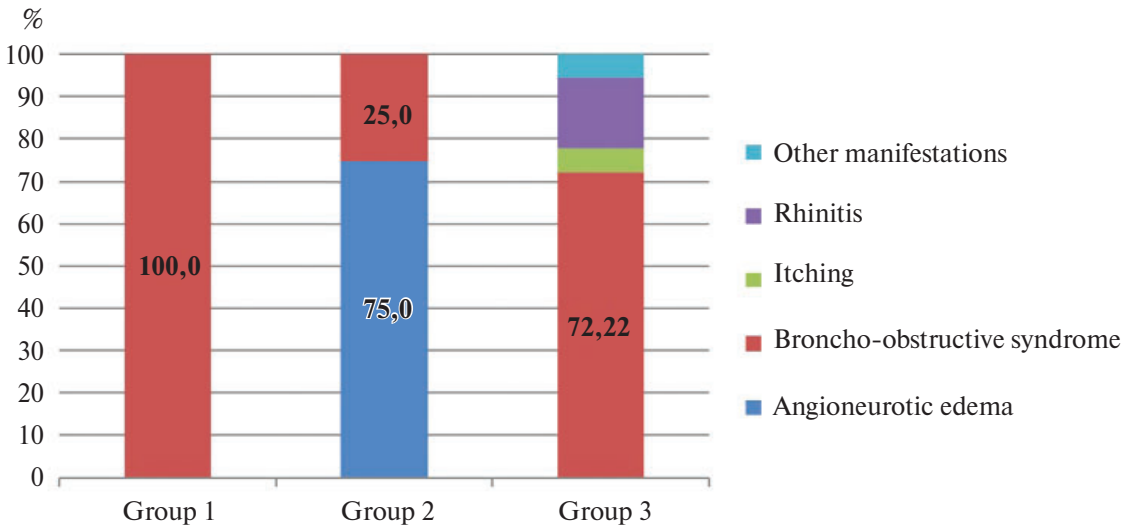

Fig. 5. Structure of clinical manifestations of drug intolerance to angiotensin-converting enzyme inhibitors in three age groups.

Somatic pathology and allergies

The presence of somatic pathology of three or more systems in combination with age did not show a meaningfully significant opportunity to increase the amount of drugs to which drug-induced hypersensitivity reactions may occur; also, this criterion did not aggravate the clinical manifestations of drug intolerance, as patients with drug-induced anaphylactic shock had both the somatic pathology of three or more systems and a less significant comorbid background. The presence of allergic pathology both separately and in combination with somatic pathology of three or more systems, both in older and younger patients also did not reveal a clinically significant increase in the severity and number of drug intolerance reactions.

Additional research outcomes

Clinical manifestations of adverse drug reactions

Clinical manifestations of drug reactions in all three groups were more often defined as angioneurotic edema (22.11%) and dermatitis (20.03%). Other reactions were less common, including other manifestations of drug reactions (16.93%), urticaria (14.68%), cough and choking (10.54%), anaphylactic shock (11.92%), itching (2.07%), and rhinitis (1.73%) (Fig. 6; Table 3).

Drugs

A total of 515 drugs were identified, which induced adverse reactions. Further, we distributed them into 33 groups according to the clinical and pharmacological classification. We selected 11 groups (in decreasing incidence) of them, which were antibiotics (19.19%), local anesthetics (11.82%), nonsteroidal anti-inflammatory

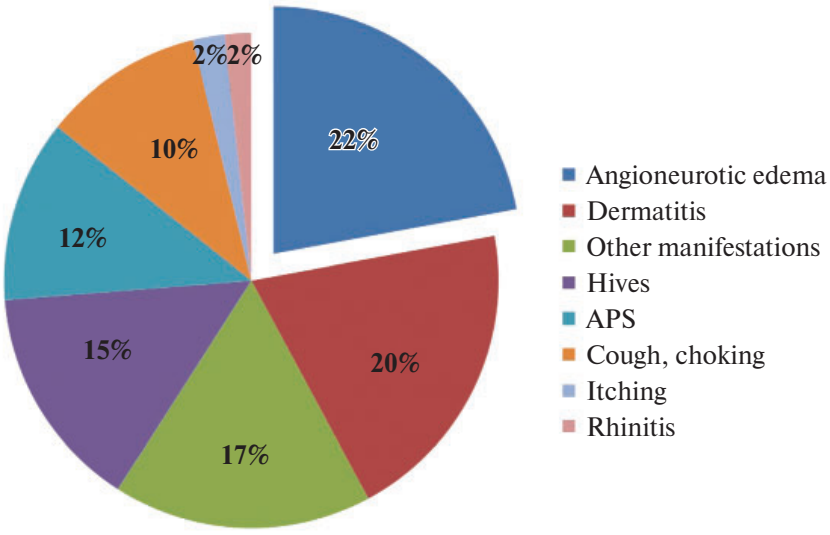

Fig. 6. The overall structure of clinical manifestations of drug reactions;
Note. АФШ — anaphylactic shock. This diagram does not include cough on angiotensin-converting enzyme inhibitors.

 DOI: https://doi.org/10.36691/RJA1436

Table 5. Groups of drugs for which drug hypersensitivity reactions occurred most frequently in the whole sample

Clinical and pharmacological group of the drug	Incidence of drug hypersensitivity reactions
Antibiotics, *n* (%)	99 (19.9)
Local anesthetics, *n* (%)	61 (11.82)
NSAIDs, *n* (%)	58(11.24)
B vitamins, *n* (%)	41 (7.95)
Iodine-contrast agents, *n* (%)	23 (4.46)
Non-narcotic analgesics, *n* (%)	22 (4.26)
Angiotensin-converting enzyme inhibitors, *n* (%)	21 (4.07)
Antihistamines, *n* (%)	16 (3.1)
Macro- and microelements, *n* (%)	13 (2.52)
Muscle relaxants, *n* (%)	12 (2.33)
Animal origin drugs, *n* (%)	11 (2.13)
Others, *n* (%)	139 (26.94)

Note. NSAIDs — nonsteroidal anti-inflammatory drugs.

drugs (11.24%), B vitamins (7.95%) , iodine preparations (4.46%), ACE inhibitors (4.07%), antihistamines (3.1%), macro and microelements (2.52%), muscle relaxants (2.33%), animal origin products (2.13%). The others (26.94%) included drugs whose incidence of reactions was less than 2% (Table 5; Fig. 3).

Antibacterial drugs

In the range of the clinical manifestations of drug-induced hypersensitivity to antibacterial drugs, reactions in the form of dermatitis (31.4%) and angioneurotic edema (23.14%) were most common in the general sample; while manifestations in the form of rhinitis were not recorded.

In the range of the most common hypersensitivity reactions to penicillins in the general sample, dermatitis (36.21%), angioneurotic edema (20.69%), and urticaria (20.69%) were identified. On the other hand, hypersensitivity reactions to cephalosporins differed and manifested as anaphylactic shock (40%), angioneurotic edema (28%), and urticaria (12%).

Adverse events

During the study, no adverse events were registered.

Discussion

Summary of the main research outcome

The patient's age does not affect the possibility of reactions to certain groups of drugs (except for ACE inhibitors, which was most likely due to the higher frequency of prescribing antihypertensive therapy in patients of this age group). Aggravation of clinical manifestations and the occurrence of polypragmasy are not associated with age or comorbid background. The correlation dependence between age and non-life-threatening clinical manifestations of drug-induced hypersensitivity indicates the absence of a significant effect of age on the possibility of anaphylactic shock or angioneurotic edema.

A high percentage of identified reactions to local anesthetics was associated to a greater extent with vasovagal reactions (33.87% of patients noted reactions in the form of fainting or precollaptoid state) than with hypersensitivity reactions.

Most of the reactions, in the form of anaphylactic shock, were not documented, and the patient could misinterpret the condition that arose, which could affect the results.

Research limitations

Pharmacological and allergic history data were indicated only based on the information received from the patient and, possibly, a diagnosis of drug-induced hypersensitivity previously made in another healthcare facility. Furthermore, when planning and conducting the study, the sample size was not calculated to achieve the required statistical power of the results. In this regard, the sample of participants obtained during the study cannot be considered sufficiently representative, which does not enable extrapolating the results obtained and their interpretation (conclusions) to the general population of similar patients beyond the study.

Conclusion

The influence of age as a risk factor for the development of drug-induced hypersensitivity is not completely understood. According to our data, in all patients, regardless of age, adverse reactions occurred with approximately the same frequency to antibiotics, nonsteroidal anti-inflammatory drugs, local anesthetics, B vitamins, non-narcotic analgesics, which indicates that age does not influence the risk of reactions to certain groups of drugs. The revealed significant differences in ACE inhibitors are associated with the high frequency and duration of their use by elderly and senile people. Elderly patients also have some aspects of the clinical manifestations of adverse reactions to drugs, which may be associated with the presence of combined comorbid conditions and the peculiarities of their therapeutic correction. Such pa-

tients require more careful attention from primary care physicians when prescribing therapy to avoid possible cross-effects of a number of drugs.

Additional information

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare no obvious and potential conflicts of interest related to the publication of this article.

Authors' contribution. O.A. Rychkova — concept and design of the study; A.V. Brown, M.A. Nesterova — collection and processing of materials; M.A. Grakhova, A.S. Sagitova — collection of materials, analysis of obtained data and drafting. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. Khaitov RM, Ilyina NI, editors. Allergology and immunology: national guidelines. Moscow: GEOTAR-Media; 2012. 634 p. (In Russ).
2. Montanez MI, Mayorga C, Bogas G, et al. Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis. *Front Immunol*. 2017;(8):614. doi: 10.3389/fimmu.2017.00614
3. Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am*. 2009;29(3):405–418. doi: 10.1016/j.iac.2009.04.005
4. Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Textbook of adverse drug reactions. Davies D.M., editor. Oxford: Oxford University Press; 1991.
5. Khaitov RM, editor. Drug allergy: guidelines for physicians. Moscow: Farmarus Print Media; 2012. 126 p. (In Russ).
6. Bulgakova VA, Eliseeva TI, Balabolkin II, Smirnov IE Mechanisms of development, opportunities for diagnostics, treatment, and prevention of allergic responses to drugs (review). *Russian Pediatric Journal*. 2019;22(1):42–50.(In Russ). doi: 10.18821/1560-9561-2018-22-1-42-50
7. Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(2):126–137. doi: 10.1016/j.jaci.2009.10.028
8. Myasnikova TN, Romanova TS, Khludova LG, Latysheva TV. Diagnosis of drug allergy: a current view of the problem. *RMJ*. 2018;(8):28–32. (In Russ).
9. Koransky R, Ferastraoaru D, Jerschow E. Single nonsteroidal anti-inflammatory drug induced serum sickness-like reaction to naproxen in a patient able to tolerate both aspirin and ibuprofen. *J Allergy Clin Immunol Pract*. 2016;4(1):160–161. doi: 10.1016/j.jaip.2015.07.019
10. Torres MJ, Adkinson NF, Caubet JC, et al. Controversies in drug allergy: beta-lactam hypersensitivity testing. *J Allergy Clin Immunol Pract*. 2019;7(1):40–45. doi: 10.1016/j.jaip.2018.07.051
11. Castellazzi ML, Esposito S, Claut LE, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in two young children: the importance of an early diagnosis. *Ital J Pediatr*. 2018;44(1):93. doi: 10.1186/s13052-018-0535-4
12. Clark S, Wei W, Rudders SA, Camargo CA. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. *J Allergy Clin Immunol*. 2014;134(5):1125–1130. doi: 10.1016/j.jaci.2014.05.018
13. Brown SG, Stone SF, Fatovich DM, et al. Anaphylaxis: clinical patterns, mediator release, and severity. *J Allergy Clin Immunol*. 2013;132(5):1141–1149. doi: 10.1016/j.jaci.2013.06.015
14. Cavkaytar O, Karaatmaca B, Cetinkaya PG, et al. Characteristics of drug-induced anaphylaxis in children and adolescents. *Allergy Asthma Proceedings*. 2017;38(5):56–63. doi: 10.2500/aap.2017.38.4064
15. Oussalah A, Mayorga C, Blanca M, et al. Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review. *Allergy*. 2016;71(4):443–462. doi: 10.1111/all.12821

ЛИТЕРАТУРА

1. Аллергология и иммунология: Национальное руководство / под ред. Р.М. Хаитова, Н.И. Ильиной. Москва: ГЭОТАР-Медиа, 2013. 634 с.
2. Montanez M.I., Mayorga C., Bogas G., et al. Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis // Front Immunol. 2017. Vol. 8. P. 614. doi: 10.3389/fimmu.2017.00614
3. Schnyder B. Approach to the patient with drug allergy // Immunol Allergy Clin North Am. 2009. Vol. 29, N 3. P. 405–418. doi: 10.1016/j.iac.2009.04.005
4. Rawlins M.D., Thompson J.W. Mechanisms of adverse drug reactions. In: Textbook of adverse drug reactions. Davies D.M., editor. Oxford: Oxford University Press; 1991. P. 18–45.
5. Лекарственная аллергия. Методические рекомендации для врачей / под ред. Р.М. Хаитова. Москва: Фармарус Принт Медиа, 2012. 126 с.
6. Булгакова В.А., Елисеева Т.И., Балаболкин И.И., Смирнов И.Е. Особенности развития, диагностика, лечение и профилактика аллергических реакций на лекарства // Российский педиатрический журнал. 2019. Т. 22, № 1. С. 42–50. doi: 10.18821/1560-9561-2019-22-1-42-50
7. Khan D.A., Solensky R. Drug allergy // J Allergy Clin Immunol. 2010. Vol. 125, N 2, Suppl 2. P. 126–137. doi: 10.1016/j.jaci.2009.10.028
8. Мясникова Т.Н., Романова Т.С., Хлудова Л.Г., Латышева Т.В. Диагностика лекарственной аллергии: современный взгляд на проблему // РМЖ. 2018. № 8. С. 28–32.
9. Koransky R., Ferastraoaru D., Jerschow E. Single nonsteroidal anti-inflammatory drug induced serum sickness-like reaction to naproxen in a patient able to tolerate both aspirin and ibuprofen // J Allergy Clin Immunol Pract. 2016. Vol. 4, N 1. P. 160–161. doi: 10.1016/j.jaip.2015.07.019
10. Torres M.J., Adkinson N.F., Caubet J.C., et al. Controversies in drug allergy: beta-lactam hypersensitivity testing // J Allergy Clin Immunol Pract. 2019. Vol. 7, N 1. P. 40–45. doi: 10.1016/j.jaip.2018.07.051
11. Castellazzi M.L., Esposito S., Claut L.E., et al. Drug reaction with eosinophilia and systemic symptoms (DR ESS) syndrome in two young children: the importance of an earlydiagnosis // Ital J Pediatr. 2018. Vol. 44, N 1. P. 93. doi: 10.1186/s13052-018-0535-4

12. Clark S., Wei W., Rudders S.A., Camargo C.A. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatmentin US emergency departments and hospitals // J Allergy Clin Immunol. 2014. Vol. 134, N 5. P. 1125–1130. doi: 10.1016/j.jaci.2014.05.018
13. Brown S.G., Stone S.F., Fatovich D.M., et al. Anaphylaxis: clinical patterns, mediator release, and severity // J Allergy Clin Immunol. 2013. Vol. 132, N 5. P. 1141–1149. doi: 10.1016/j.jaci.2013.06.015
14. Cavkaytar O., Karaatmaca B., Cetinkaya P.G., et al. Characteristics of drug-induced anaphylaxis in children and adolescents // Allergy Asthma Proceedings. 2017. Vol. 38, N 5. P. 56–63. doi: 10.2500/aap.2017.38.4064
15. Oussalah A., Mayorga C., Blanca M., et al. Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review // Allergy. 2016. Vol. 71, N 4. P. 443–462. doi: 10.1111/all.12821

AUTHORS' INFO

Corresponding author:
Maria A. Grakhova, MD;
address: 55 Kotovskogo, 625023 Tyumen, Russia;
ORCID: http://orcid.org/0000-0002-1657-0695;
eLibrary SPIN: 3567-8379;
e-mail: mari.grahova@yandex.ru

Co-authors:
Olga A. Rychkova, MD, Dr. Sci. (Med.), Professor;
ORCID: http://orcid.org/0000-0002-2566-5370;
eLibrary SPIN: 1382-1555; e-mail: richkovaoa@mail.ri

Almira S. Sagitova, MD, Cand. Sci. (Med.);
ORCID: http://orcid.org/0000-0002-6741-8458;
eLibrary SPIN: 8210-5726; e-mail: ya.al.sagitowa@yandex.ru

Anastasia V. Braun, MD;
ORCID: https://orcid.org/0000-0002-5909-2048;
eLibrary SPIN: 8332-6947;
e-mail: badulina_anastasiya@mail.ru

Maria A. Nesterova, MD;
ORCID: https://orcid.org/0000-0002-0668-6213;
eLibrary SPIN: 2103-4460;
e-mail: maria.nesterova72@yandex.ru

ОБ АВТОРАХ

Автор, ответственный за переписку:
Грахова Мария Андреевна;
адрес: Россия, 625023, Тюмень, ул. Котовского, д. 55;
ORCID: http://orcid.org/0000-0002-1657-0695;
eLibrary SPIN: 3567-8379;
e-mail: mari.grahova@yandex.ru

Соавторы:
Рычкова Ольга Александровна, д.м.н., профессор;
ORCID: http://orcid.org/0000-0002-2566-5370;
eLibrary SPIN: 1382-1555; e-mail: richkovaoa@mail.ri

Сагитова Альмира Самигулловна, к.м.н.;
ORCID: http://orcid.org/0000-0002-6741-8458;
eLibrary SPIN: 8210-5726; e-mail: ya.al.sagitowa@yandex.ru

Браун Анастасия Викторовна;
ORCID: https://orcid.org/0000-0002-5909-2048;
eLibrary SPIN: 8332-6947;
e-mail: badulina_anastasiya@mail.ru

Нестерова Мария Александровна;
ORCID: https://orcid.org/0000-0002-0668-6213;
eLibrary SPIN: 2103-4460;
e-mail: maria.nesterova72@yandex.ru

DOI: https://doi.org/10.36691/RJA1465

New opportunities of therapy of severe atopic dermatitis

I.V. Demko[1, 2], E.A. Sobko[1, 2], A.Yu. Kraposhina[1, 2], N.A. Shestakova[1, 2], N.V. Gordeeva[1, 2], K.F. Kasymova[1]

[1] Professor V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, Russian Federation
[2] Krasnoyarsk Clinical Regional Hospital, Krasnoyarsk, Russian Federation

ABSTRACT

This article presents a case of the successful use of dupilumab in a 21-year-old patient with severe atopic dermatitis, concomitant bronchial asthma, and allergic rhinitis. The patient was observed in the allergological department of the Krasnoyarsk Clinical Regional Hospital for 2 years. The disease was characterized by constant skin symptoms, frequent exacerbations, resistance to standard therapy, including systemic glucocorticosteroids and immunosuppressors. Considering the above factors, targeted therapy was started with dupilumab, registered in the Russian Federation for use in atopic dermatitis resistant to standard therapy. Against the background of biological therapy (13 injections were carried out), a stable significant decrease in skin syndrome activity was achieved (SCORAD index decreased from 72 to 9 points), and the patient's quality of life significantly improved.

Keywords: atopic dermatitis; biological therapy; dupilumab; case report

For citation: Demko IV, Sobko EA, Kraposhina AYu, Shestakova NA, Gordeeva NV, Kasymova KF. New opportunities of therapy of severe atopic dermatitis. *Russian Journal of Allergy*. 2021;18(3):113–119. DOI: https://doi.org/10.36691/RJA1465

Новые возможности терапии тяжёлого атопического дерматита

И.В. Демко[1, 2], Е.А. Собко[1, 2], А.Ю. Крапошина[1, 2], Н.А. Шестакова[1, 2], Н.В. Гордеева[1, 2], К.Ф. Касымова[1]

[1] Красноярский государственный медицинский университет имени профессора В.Ф. Войно-Ясенецкого, Красноярск, Российская Федерация
[2] Красноярская краевая клиническая больница, Красноярск, Российская Федерация

АННОТАЦИЯ

Представлен случай успешного применения препарата дупилумаб у 21-летнего пациента с тяжёлым атопическим дерматитом, сопутствующей бронхиальной астмой и аллергическим ринитом. Пациент наблюдался в аллергологическом отделении КГБУЗ «Красноярская краевая клиническая больница» в течение 2 лет. Заболевание характеризовалось постоянными кожными симптомами, частыми обострениями, устойчивостью к стандартной терапии, в том числе системными глюкокортикоидами и иммуносупрессивными препаратами. Учитывая вышеперечисленные факторы, было принято решение о начале таргетной терапии дупилумабом, зарегистрированным в Российской Федерации для применения при атопическом дерматите, резистентном к стандартному протоколу лечения. На фоне введения препарата (13 процедур) достигнуто стойкое значимое снижение активности кожного синдрома (снижение индекса SCORAD с 72 до 9 баллов) и значительное улучшение качества жизни пациента.

Ключевые слова: атопический дерматит; биологическая терапия; дупилумаб; клинический случай

Для цитирования: Демко И.В., Собко Е.А., Крапошина А.Ю., Шестакова Н.А., Гордеева Н.В., Касымова К.Ф. Новые возможности терапии тяжёлого атопического дерматита // *Российский аллергологический журнал*. 2021. Т. 18. № 3. С. 113–119. DOI: https://doi.org/10.36691/RJA1465

Статья поступила 26.05.2021 | Принята к печати 08.09.2021 | Опубликована 15.09.2021
Received: 26.05.2021 | Accepted: 08.09.2021 | Published: 15.09.2021

Background

Atopic dermatitis remains a complicated issue in allergology. The incidence of this disease is up to 20% in children and 2-8% in adults [1]. There has been a 2.1-fold increase in the incidence of atopic dermatitis over the past 16 years. Severe atopic dermatitis is not a life-threatening condition, however, it seriously affects the patients' quality of life [2]. Despite the development

of new therapeutic options for severe atopic dermatitis, long-term disease control cannot be achieved so far.

In recent years, special attention has been paid to the use of genetically engineered biologics, monoclonal antibodies that inhibit the key inflammatory cytokines and their receptors [3–5]. Due to their selective effects, biologics are not associated with adverse effects that are common for conventional drugs used in the treatment of allergic diseases (i.e. disorders of carbohydrate and mineral metabolism; atrophic skin changes; suppression of hematopoiesis; secondary immunodeficiency, etc.) — glucocorticoids and immunosuppressive agents.

Currently, only one genetically engineered biologic, dupilumab, is approved in the Russian Federation for the treatment of atopic dermatitis. It is approved as treatment for patients with moderate to severe atopic dermatitis with inadequate response to topical agents in patients over 6 years of age. The mechanism of action of dupilumab is the inhibition of interleukin (IL) 4 and 13-mediated signaling pathways by its specific binding to the IL-4Ra-a subunit, which is common for the IL-4 and IL-13 receptor complexes. IL-4 and IL-13 are known to be key cytokines of T2-mediated inflammatory response that is typical for atopic disorders. Multicenter clinical studies have demonstrated the effectiveness of dupilumab in the treatment of atopic dermatitis [6-8].

Case report

A 20-year-old male patient presented to Allergy Unit of RSBHI "Krasnoyarsk Regional Clinical Hospital" complaining of generalized itchy skin rash causing a sleep disorder, intermittent nasal obstruction, episodes of sneezing and rhinorrhea when contacting with animals (dogs, cats) and in the spring during the flowering of trees. There were also episodes of difficulty with breathing.

The analysis of medical history and pediatric health records showed that the first signs of atopic dermatitis had developed during infancy with episodic involvement of large skin areas. Starting from the age of 3 years, the symptoms became mild (the skin lesions were mainly located in the area of elbow joints) and increased after consumption of large amounts of citruses or sweet dishes. At the age of 3 years, the patient started experiencing symptoms of rhinitis, conjunctivitis, difficulties with breathing when contacting with animals (a cat, a dog, or a rabbit). At the same age, the patient was diagnosed with asthma. Episodes of suffocation were rare; the patient did not receive basic asthma treatment and used salbutamol on demand. At the age of 4 years, the patient started experiencing symptoms of hay fever (rhinitis, conjunctivitis). The patient was followed up by a pediatric allergist who diagnosed sensitization to pollen (birch, wormwood) and epidermal (cat, dog, rabbit) allergens. There were signs of cross-reactivity when eating peas or almond (itching and throat discomfort) and drug intolerance (cefotaxime and penicillin caused an itchy skin rash). The patient did not have a family history of atopic diseases, nor had he any signs of infestations. The patient received therapy with antihistamines and cromones, and used short-acting beta-agonists on demand. At the age of 7 years, the patient received two courses of the allergy medicine Ruzam, which resulted in some improvement: signs of atopic dermatitis and hay fever became minimal in the spring; the patient stopped having episodes of suffocation and did not require therapy with short-acting bronchodilators. He was considered to have steady asthma remission. During the adolescence, the patient noted the development of pronounced skin manifestations in the hands, elbows and popliteal regions. Therapy with emollients and topical steroids resulted in a moderate improvement.

At the age of 18, the patient's atopic dermatitis became significantly more severe with involvement of large areas of the skin: in addition to the hands, elbows and popliteal regions, skin lesions also spread to his face, ears, neck, scalp, trunk, buttocks, thighs, and the dorsal surface of the feet. In October 2018 and November 2019, due to the exacerbation of the disease, the patient received inpatient treatment in a Clinic of Dermatology and Venereal Diseases using systemic and topical glucocorticoids, antihistamines, emollients, which resulted in incomplete brief improvement. In December 2019, due to a disease exacerbation, the patient was hospitalized to Department of Allergy of Krasnoyarsk Regional Clinical Hospital.

Results of physical examination, laboratory tests, investigations and allergy tests

On admission: erythematous squamous skin lesions on the back, abdomen, chest, shoulders, forearms, buttocks, thighs; the skin in these areas appears thickened, the skin markings are increased in some areas; the eyelids, forehead, and cheeks demonstrate a slight hyperpigmentation, hyperemia, and peeling. There is an increase in the skin markings, mild hyperemia and excoriations on the dorsal surface of the feet. SCORing of Atopic Dermatitis (SCORAD) index = 72 points, which corresponds to severe atopic dermatitis.

The peripheral lymph nodes are not enlarged. Signs of nasal obstruction. Auscultation reveals vesicular breath sounds without any rhonchi. Respiratory rate is 16 breaths per minute; blood oxygen saturation (SaO_2) 98%. Clear heart sounds, no murmurs, regular rhythm; HR = 79 bpm; BP 105/75 mm Hg.

Abdominal palpation is painless and unremarkable.

Laboratory tests showed an increased eosinophil count in the peripheral blood (12.9%; 780 cells/μL) and an increased total IgE level (482 IU/mL).

X-ray examination of the paranasal sinuses showed no abnormalities; chest X-ray exam revealed no pulmonary lesions, normal structure of the roots of the lungs and bronchovascular markings; no midline shift; well-defined and smooth contour of the diaphragm and no signs of pleural effusion.

Spirometry Baseline parameters: Forced Vital Capacity (FVC) 93.5%; Forced Expiratory Volume in first

second (FEV1) 88.8%, FEV_1/FVC 80.8%. 20 min after the use of salbutamol 400 μg: FVC 93.6%, FEV1 90.1%, FEV1/FVC 81.9%. Conclusion: pulmonary ventilation parameters are within the normal range. The bronchodilator test result is negative; FEV1 increase after the use of salbutamol 400 μg is 1.5%.

Allergy testing ImmunoCAP test confirmed the sensitization to allergens of birch, pollen of a mixture of herbs, cat and dog hair, and hazelnuts.

Treatment

The patient received a course of treatment with topical and systemic glucocorticoids (prednisolone 60 mg IV), antihistamines (loratadine 10 mg/day), and emollients. Due to weak response to therapy, such therapeutic options as a calcineurin inhibitor (tacrolimus) and immunosuppressive medications (cyclosporin 200 mg/day) were also used and produced an incomplete improvement. SCORAD index at the time of discharge was 15.3. Recommended outpatient therapy included topical therapy with mometasone furoate, tacrolimus, cyclosporin at a dose of 100 mg twice daily (daily dosage = 200 mg) with an allergist consultation once a month for the assessment of treatment response and treatment adjustment if necessary. One month after the discharge from the hospital, the cyclosporin dose was reduced to 150 mg/day, and 2 months after the discharge it was decreased to 100 mg/day.

Despite the combination therapy used, no steady improvement was observed, and there were persistent recurrences of atopic dermatitis. In September 2020, the patient was admitted to Allergy Unit again with severe manifestations of dermatitis (SCORAD = 64), debilitating pruritus and a sleep disorder. Taking into account the severe course of the disease, frequent exacerbations (4 exacerbations in 2020), the lack of a stable effect from conventional therapy and immunosuppressive drugs, frequent use of systemic glucocorticoids, concomitant allergic rhinitis and asthma (in remission), it was decided to use the genetically engineered drug dupilumab. As recommended in the prescribing information, the initial dose was 600 mg (two 300 mg SC injections) followed by 300 mg SC once every two weeks. No adverse drug reactions were observed.

Outcome and follow-up results

While on therapy with dupilumab (a total of 13 injections), there was clear improvement (significant regression of skin lesion and pruritus, as well as sleep normalization). SCORAD index by the 13th dosing was 9 points (see Fig. 1).

During the entire follow-up period, the patient did not have any exacerbations of allergic rhinitis or signs of nasal obstruction, and experienced no shortness of breath. The treatment was considered to be effective and was continued.

With regard to biomarkers of T2-mediated inflammation, we evaluated the peripheral blood eosinophil count before each drug dosing and the total IgE level before the drug dosing and after 8th dosing (for technical reasons). During dupilumab therapy, the eosinophil count increased reaching its peak by the 4th dosing, and then started decreasing reaching 71% of the baseline value by the 13th dosing (without reaching the normal range) (see Fig. 2). Baseline total IgE level was 482 IU/mL, and decreased to 458 IU/mL after the 8th dupilumab dosing.

Discussion

Classical manifestations of the atopic march include signs of atopic dermatitis with subsequent development of food allergy, allergic rhinitis and, finally, asthma. These disorders are due to a persistent T2-mediated immune response, the laboratory manifestations of which include peripheral blood eosinophilia and increased total immunoglobulin E level (IgE) [9]. To date, there is evidence of concomitant development of skin manifestations and airway obstruction in some patients.

In our case report, the patient demonstrated classical features of T2-dysfunction that started from the skin involvement and early development of allergic rhinitis

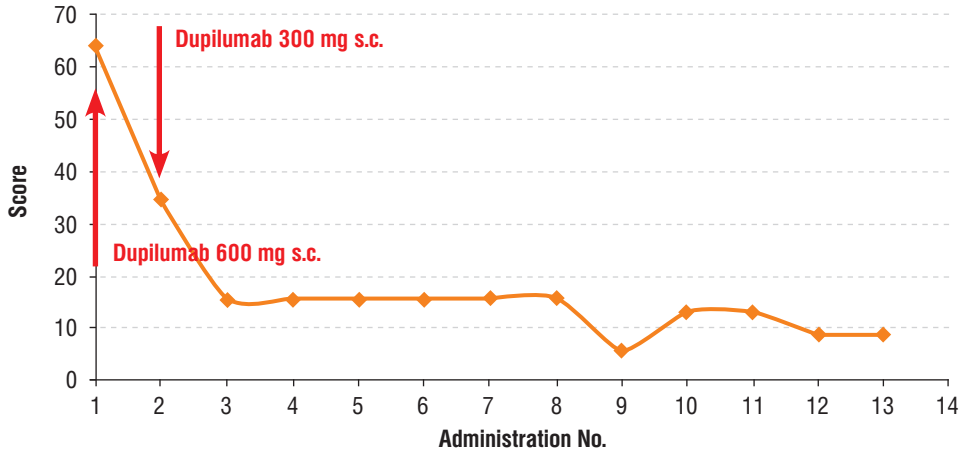

Fig. 1. Disease activity (SCORAD) against background of dupilumab use

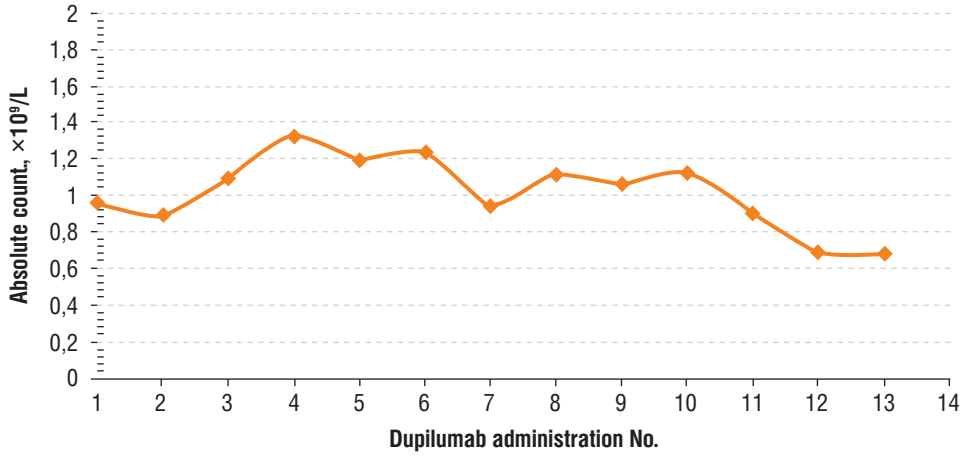

Fig. 2. Number of eosinophils in peripheral blood against background of dupilumab preparation application

and asthma. Despite the use of adequate therapy for associated allergic disorders and the patient's compliance with the recommendations on hypoallergenic lifestyle and diet, it was not possible to achieve stable control over his symptoms. Frequent recurrences of atopic dermatitis, starting from adolescence, with generalization of the skin process, accompanied by pronounced sleep disorders and a decrease in physical activity, required long-term use of not only topical, but also systemic glucocorticoids, and immunosuppressive drugs. Given the comorbidity of the disorder, the risks of asthma exacerbations in case of comorbid severe atopic dermatitis are increased. Due to the availability of the new genetically engineered drug dupilumab for the treatment of moderate to severe atopic dermatitis in patients over 6 years of age, a decision was made to use it in our patient as he had other T2-mediated allergic disorders (allergic rhinitis, atopic asthma) [6, 11, 12]. There was a significant clinical improvement even after first injections of dupilumab with no adverse drug reactions indicating a high effectiveness and safety of the drug.

Markers of T2 inflammation, the peripheral blood eosinophil count and total IgE concentration, were assessed in this case. In this case report, peripheral blood eosinophil counts were increasing while on therapy with dupilumab and reached a peak at Week 8 of treatment. They decreased later, which is consistent with the data of placebo-controlled clinical studies that also showed a transient increase in the blood eosinophil count, despite the positive clinical effect of dupilumab therapy in patients with atopic dermatitis. Studies with dupilumab in asthma patients have shown that the reduction in the severity of eosinophilic inflammation in the lungs occurs regardless of the blood eosinophil count (normal or increased), and is also associated with clinical improvement [3, 12]. A temporary increase in the blood eosinophil count may be related to the dupilumab-induced inhibition of eosinophil migration to the tissue by suppressing IL-4 and IL-13-mediated production of eotaxins and vascular cell adhesion molecule 1 (VCAM-1), while the drug does not affect the production or release of eosinophils from the bone marrow [13].

The comparison of the total IgE levels at baseline and after 16 weeks of treatment in our patient demonstrates that this parameter tended to decrease; however, its further monitoring is necessary, since it was previously shown that the decrease in total IgE, unlike other biomarkers of T2 inflammation (e.g. periostin, pro-inflammatory cytokines and thymus and activation-regulated chemokine, TARC), although slower, is by more than 70% at Week 52 of treatment, which is associated with impaired B-cell proliferation and IgE secretion as a result of IL-4 binding impairment caused by dupilumab [11, 14].

Thus, the availability of genetically engineered biologics for the treatment of atopic dermatitis expands the range of treatment options for patients with moderate to severe course of disease resistant to conventional treatment, and allows improving their quality of life, reducing the risk of adverse effects of systemic glucocorticoids and immunosuppressive medications [15, 16].

Conclusion

This case report is interesting as assessment of the response to treatment for atopic dermatitis concomitant with other allergic diseases. Based on our experience and the experience of other authors, we recommend considering targeted therapy in patients with severe atopic dermatitis with a weak response to conventional treatment regimens.

Increasing evidence related to the use of dupilumab will enable evaluation of its effectiveness in patients with atopic dermatitis and other T2-mediated allergic diseases.

Additional information

Funding source. This article was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. I.V. Demko — editing the article; E.A. Sobko — patient management, editing the article; A.Yu. Kraposhina, N.A. Shestakova — preparation and writing the text of the article; N.V. Gordeeva — writing the text of the article; K.F. Kasymova — collection and analysis of literary sources. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. Written consent for publication of relevant medical information within the manuscript was obtained from the patient.

REFERENCES

1. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol.* 2018;32(5):657–682. doi: 10.1111/jdv.14891
2. Kozyeva VV. Prevalence of bronchial asthma and atopic dermatitis in children. *Allea nauki.* 2017;3(9):469–472. (In Russ).
3. Dyneva ME, Aminova GE, Kurbacheva OM, et al. Dupilumab: new opportunities for the treatment of asthma and chronic rhinosinusitis with nasal polyps. *Russian Journal of Allergy.* 2021;18(1):18–31. (In Russ). doi: 10.36691/RJA1408
4. Smolkin YS, Balabolkin II, Gorlanov IA, et al. Consensus document APAIR: atopic dermatitis in children — update 2019 (short version). Part 1. *Allergol Immunol Pediatr.* 2020;60(1):4–25. doi: 10.24411/2500-1175-2020-10001
5. Snast I, Reer O, Hodak E, et al. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. *Am J Clin Dermatol.* 2018;19(2):145–165. doi: 10.1007/s40257-017-0324-7
6. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016;375(24):2335–2348. doi: 10.1056/NEJMoa1610020
7. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287–2303. doi: 10.1016/S0140-6736(17)31191-1
8. Thaçi D, Simpson E, Deleuran M, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *J Dermatol Sci.* 2019;94(2):266–275. doi: 10.1016/j.jdermsci.2019.02.002
9. Lowe AJ, Leung DY, Tang ML, et al. The skin as a target for prevention of the atopic march. *Ann Allergy Asthma Immunol.* 2018;120(2):145–151. doi: 10.1016/j.anai.2017.11.023
10. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol.* 2006;118(1):209–213. doi: 10.1016/j.jaci.2006.04.043
11. Smolkin YS, Masalsky SS, Smolkina OY. The application of the biological treatment in atopic dermatitis: focus on dupilumab. *Allergology and Immunology in Pediatrics.* 2020;61(2):27–40. (In Russ). doi: 10.24411/2500-1175-2020-10005
12. Zayed Y, Kheiri B, Banifadel M, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma.* 2019;56(10):1110–1119. doi: 10.1080/02770903.2018.1520865
13. Tozawa H, Kanki Y, Suehiro J, et al. Genome-wide approaches reveal functional interleukin-4-inducible STAT6 binding to the vascular cell adhesion molecule 1 promoter. *Mol Cell Biol* 2011;31(11):2196–2209. doi: 10.1128/MCB.01430-10
14. Mineev VN, Sorokina LN, Trofimov VI, et al. Interleukin-4 and interleukin-13 receptors: structure, function and genetic polymorphism. *Pulmonology.* 2010;(3):113–119. (In Russ).
15. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. *J Am Acad Dermatol.* 2018;78(1):62–69. doi: 10.1016/j.jaad.2017.09.052
16. Balabolkin II, Terletskaya RN, Modestov AA. Allergic morbidity of children in modern environmental conditions. *Siberian Medical Review.* 2015;91(1):63–67. (In Russ).

ЛИТЕРАТУРА

1. Wollenberg A., Barbarot S., Bieber T., et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I // J Eur Acad Dermatol Venereol. 2018. Vol. 32, N 5. P. 657–682. doi: 10.1111/jdv.14891
2. Козьева В.В. Распространенность бронхиальной астмы и атопического дерматита у детей // Аллея науки. 2017. Т. 3, № 9. С. 469–472.
3. Дынева М.Е., Аминова Г.Э., Курбачева О.М., Ильина Н.И. Дупилумаб: новые возможности в терапии бронхиальной астмы и полипозного риносинусита // Российский аллергологический журнал. 2021. Т. 18, № 1. С. 18–31. doi: 10.36691/RJA1408
4. Смолкин Ю.С., Балаболкин И.И., Горланов И.А., и др. Согласительный документ АДАИР: атопический дерматит у детей — обновление 2019 (краткая версия). Часть 1 // Аллергология и иммунология в педиатрии. 2020. Т. 60, № 1. С. 4–25. doi: 10.24411/2500-1175-2020-10001
5. Snast I., Reer O., Hodak E., et al. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis // Am J Clin Dermatol. 2018. Vol. 19, N 2. P. 145–165. doi: 10.1007/s40257-017-0324-7
6. Simpson E.L., Bieber T., Guttman-Yassky E., et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis // N Engl J Med. 2016. Vol. 375, N 24. P. 2335–2348. doi: 10.1056/NEJMoa1610020
7. Blauvelt A., de Bruin-Weller M., Gooderham M., et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial // Lancet. 2017. Vol. 389, N 10086. P. 2287–2303. doi: 10.1016/S0140-6736(17)31191-1
8. Thaçi D., Simpson E., Deleuran M., et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2) // J Dermatol Sci. 2019. Vol. 94, N 2. P. 266–275. doi: 10.1016/j.jdermsci.2019.02.002
9. Lowe A.J., Leung D.Y., Tang M.L., et al. The skin as a target for prevention of the atopic march // Ann Aller-

gy Asthma Immunol. 2018. Vol. 120, N 2. P. 145–151. doi: 10.1016/j.anai.2017.11.023
10. Williams H., Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis // J Allergy Clin Immunol. 2006. Vol. 118, N 1. P. 209–213. doi: 10.1016/j.jaci.2006.04.043
11. Смолкин Ю.С., Масальский С.С., Смолкина О.Ю. Вопросы применения биологической терапии при атопическом дерматите: акцент на дупилумаб // Аллергология и иммунология в педиатрии. 2020. Т. 61, № 2. С. 27–40. doi: 10.24411/2500-1175-2020-10005
12. Zayed Y., Kheiri B., Banifadel M., et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials // J Asthma. 2019. Vol. 56, N 10. P. 1110–1119. doi: 10.1080/02770903.2018.1520865
13. Tozawa H., Kanki Y., Suehiro J., et al. Genome-wide approaches reveal functional interleukin-4-inducible STAT6 binding to the vascular cell adhesion molecule 1 promoter // Mol Cell Biol. 2011. Vol. 31, N 11. P. 2196–2209. doi: 10.1128/MCB.01430-10
14. Минеев В.Н., Сорокина Л.Н., Трофимов В.И., и др. Рецепторы к интерлейкину-4 и -13: строение, функция и генетический полиморфизм // Пульмонология. 2010. № 3. С. 113–119.
15. Fleming P., Drucker A.M. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials // J Am Acad Dermatol. 2018. Vol. 78, N 1. P. 62–69. doi: 10.1016/j.jaad.2017.09.052
16. Балаболкин И.И., Терлецкая Р.Н., Модестов А.А. Аллергическая заболеваемость детей в современных экологических условиях // Сибирское медицинское обозрение. 2015. № 1. С. 63–67.

AUTHORS' INFO

Corresponding author:
Angelina Yu. Kraposhina, MD, Cand. Sci. (Med.), Associate Professor; address: 1, Partizan Zheleznyak str., 660022, Krasnoyarsk, Russia;
ORCID: https://orcid.org/0000-0001-6896-877X;
eLibrary SPIN: 8829-9240;
e-mail: angelina-maria@inbox.ru

Co-authors:
Irina V. Demko, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0001-8982-5292;
eLibrary SPIN: 6520-3233; e-mail: demko64@mail.ru

Elena A. Sobko, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-9377-5213;
eLibrary SPIN: 9132-6756; e-mail: sobko29@mail.ru

Natalia A. Shestakova, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0002-2252-7423;
eLibrary SPIN: 4579-4502; e-mail: barsk@rambler.ru

Natalia V. Gordeeva, MD, Cand. Sci. (Med.), Associate Professor; ORCID: https://orcid.org/0000-0002-0586-8349;
eLibrary SPIN: 7914-7630; e-mail: natagorday@yandex.ru

Karina F. Kasymova, MD;
ORCID: https://orcid.org/0000-0001-8448-6113;
eLibrary SPIN: 4691-2399; e-mail: ayaneshiroi@gmail.com

ОБ АВТОРАХ

Автор, ответственный за переписку:
Крапошина Ангелина Юрьевна, к.м.н., доцент;
адрес: Россия, 660022, Красноярск,
ул. Партизана Железняка, д. 1;
ORCID: https://orcid.org/0000-0001-6896-877X;
eLibrary SPIN: 8829-9240;
e-mail: angelina-maria@inbox.ru

Соавторы:
Демко Ирина Владимировна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0001-8982-5292;
eLibrary SPIN: 6520-3233; e-mail: demko64@mail.ru

Собко Елена Альбертовна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-9377-5213;
eLibrary SPIN: 9132-6756; e-mail: sobko29@mail.ru

Шестакова Наталья Алексеевна, к.м.н.;
ORCID: https://orcid.org/0000-0002-2252-7423;
eLibrary SPIN: 4579-4502; e-mail: barsk@rambler.ru

Гордеева Наталья Владимировна, к.м.н., доцент;
ORCID: https://orcid.org/0000-0002-0586-8349;
eLibrary SPIN: 7914-7630; e-mail: natagorday@yandex.ru

Касымова Карина Фарман кызы;
ORCID: https://orcid.org/0000-0001-8448-6113;
eLibrary SPIN: 4691-2399; e-mail: ayaneshiroi@gmail.com