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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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DIAGNOSIS OF AN ALLERGIC REACTION TO ANTIBIOTICS IN AN PATIENT WITH ACTIVE HUMAN HERPESVIRUS -4, -6 TYPE INFECTION (CLINICAL CASE)

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Abstract. Beta-lactam antibiotics (BLAs) can provoke drug hypersensitivity reactions, particularly delayed-type reactions.

This article presents a case of drug allergy with manifestations of Stevens-Johnson syndrome (SJD) in a 42-year-old man with yersiniosis and active herpesvirus -4, -6 types, who received amoxacillin with clavulanic acid. The patient underwent a basophil activation test (BAT) for BLAs, and a positive result was found for both amoxacillin and 2nd and 3rd generation cephalosporins.

On the example of a clinical case, probable pathogenetic mechanisms of the risk of the appearance of immediate-type hypersensitivity reactions in persons with active herpesvirus -4, -6 type infection are shown. The possibility of using the cellular BAT for the diagnosis of delayed-type hypersensitivity reactions and for the diagnosis of cross-reactions to antibiotics has also been demonstrated.

Key words. Drug hypersensitivity reactions, Stevens-Johnson syndrome, basophil activation test, human herpesvirus -4, -6, types antibiotics cross-reactions.

ДИАГНОСТИКА АЛЛЕРГИЧЕСКОЙ РЕАКЦИИ НА АНТИБИОТИКИ В ПАЦИЕНТА С АКТИВНОЙ ГЕРПЕСВИРУСНОЙ ИНФЕКЦИЕЙ -4, -6 ТИПА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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РЕЗЮМЕ. Бета-лактамные антибиотики (БЛА) могут провоцировать реакции гиперчувствительности к лекарственным препаратам, в частности, реакции замедленного типа.

В данной статье представлен случай развития медикаментозной аллергии с проявлениями синдром Стивенса-Джонсона (ССД) у 42-летнего мужчины с иерсиниозом и активной герпесвирусной инфекцией -4, -6 типа, получавшего амоксациллин с клавулоновой кислотой. Пациенту проведен тест активации базофилов (БАТ) к БЛА и выявлен положительный результат как к амоксациллину, так и к цефалоспоринам 2 и 3 поколений.

На примере клинического случая показаны возможные патогенетические механизмы риска появления реакций гиперчувствительности немедленного типа у лиц с активной герпесвирусной инфекцией -4, -6 типа. Также была продемонстрирована возможность использования БАТ для диагностики реакций гиперчувствительности замедленного типа и диагностики перекрестных реакций на антибиотики.

Ключевые слова. Реакции гиперчувствительности к лекарственным препаратам, синдром Стивенса-Джонсона, типа, активации базофилов, вирусы герпеса человека -4, -6, типа перекрестные реакции на антибиотики.

Introduction. Beta-lactam antibiotics (BLA) are the first-choice antibiotics to treat the majority of bacterial infections [1,2] which can provoke drug hypersensitivity reactions (DHRs). BLA induces hypersensitivity reactions via specific immunologic mechanisms in all age groups [3].

Antibiotic therapy often can result in immediate-type hypersensitivity reactions [4]. DHRs can be realized by IgE-mediated or non-IgE-mediated mechanisms. IgE-mediated mechanisms are mediated by drug-specific IgE via an immune response to a hapten/carrier complex [5]. To non-IgE-mediated DHRs attribute next important immunologic mechanisms: 1) Fas-associated death domain protein (FADD) on keratinocytes leads to the extensive necrosis of epidermal cells in individuals with Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN); 2) drug-specific cytotoxic T lymphocytes (CTL) and natural killer (NK) cells play more important roles in the keratinocyte death in SJS/TEN; 3) the cytokines TNF-α, IFN-γ, TARC, IL-15 plays a crucial role in SJS/TEN, drug reaction with eosinophilia and systemic symptoms (DRESS)/ DHRs, and acute generalized exanthematous pustulosis (AGEP). The syndrome-specific effector cells: cytotoxic CD8+ T cells, NK cells producing the cytotoxic molecules, which cause extensive keratinocyte death and skin lesions in patients with SJS/TEN, moreover, the regulatory T cells (Tregs) in SJS/ TEN are inadequate [6]. Immediate reactions are most frequent when antibiotics are applied, and their stages and methods of diagnosis are thoroughly researched and described [7].

Basophils together with tissue-resident mast cells can be triggered in ways that are IgE-dependent and IgE-independent. Cross-linking of the surface-bound high-affinity IgE receptor (FcεRI) will generally occur via (glyco) proteins, chemical allergens, or autoantibodies mounted against the FcεRI or membrane-bound IgE antibodies. If not IgE-dependent, activation will mainly result from the coupling of receptors with endogenous (e.g., cytokines, anaphylatoxins, chemokines, IgG, and neuropeptides) or exogenous (e.g., pathogen-associated molecular patterns) substances [8,9].

The presence of chronic forms of viral infections is a risk factor for DHRs. They act in direct and indirect manners. Herpesviruses are associated with a break of immunoregulation and the formation of immunopathologic syndromes. Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV-6) reactivation in patients with DHRs may increase T cell activity and induce the synthesis of proinflammatory cytokines (TNF-α and IL-6). The sequential reactivations of several viruses (HHV-7, EBV,

cytomegalovirus (CMV), and coxsackievirus A6 (CVA6)) were found to be coincident with the clinical symptoms of drug hypersensitivity reactions, they may also provide exogenous peptides for presentation and participate in HLA/drug/TCR interactions [10].

Probably, the risk of DHRs is associated with the condition of immune activation, for example, in patients with unexplained fever, arthritis/arthralgia, lymphadenopathy, etc. [11].

This clinical case was used as an example to show the impact of the patient's existing immunopathology (chronic immunotropic infection, autoimmune syndrome) and increased likelihood (risk) of an allergic reaction, in this case with antibiotics. We assumed that the basophil activation test (BAT) can be used to diagnose cross-reactions between certain groups of antibiotics, as well as to establish the mechanism of formation of severe delayed-type hypersensitivity reactions to these drugs.

Case. The man was treated for yersiniosis. Augmentin 1000 mg (amoxicillin - 875.0 mg, clavulanic acid - 125.0 mg) produced by SmithKline Beecham Pharmaceuticals for GlaxoSmithKline Export Ltd, UK was prescribed twice a day for 10 days and Enterol (Saccharomyces boulardii CNCM I-745 lyophilizate), 250 mg, sorbent Eliminal gel).

On the 3rd day in the morning after consuming 4 tablets of antibiotics (8 hours after the last dose), the patient noticed haemorrhagic erosions on the mucous membranes of the mouth and genitals, and a flat red atypical spotted rash on his face (Fig.1).

The patient's body temperature rose to 38.7° C, there was a feeling of general weakness, skin pain, and pain when urinating. Subsequently, blisters filled with serous contents appeared on the mucous membranes, face skin, and palms, and skin pain intensified.

The patient was hospitalized with a diagnosis of SJS, and drug allergy. His examination revealed that the patient's condition was moderate, consciousness was not impaired, blood pressure was 130/95 mmHg, pulse rate 92 /min, and respiratory rate 25 / min.

After a thorough examination, there was no evidence of complaints and pathological symptoms from the respiratory system, cardiovascular system, and digestive tract. Palpation revealed enlargement and soreness of the submandibular and inguinal lymph nodes.

It is known from medical history that this patient has not previously had any reactions to medication and, the patient and his close relatives have no allergic diseases. The patient had a chronic low-grade fever, general weakness, fatigue, and intermittent joint pain. According to the patient, he has experienced an exacerbation of chronic tonsillitis since he was 29-32 years old 3-4 times a year, but as for reaction to his previous use of antibiotics, his answer was not certain.

Laboratory analysis:

- blood tests revealed: ESR – 36 mm/h, WBC count of 14.60 $x10^3/\mu L$ (neutrophils, $9,31x10^3/\mu L$, lymphocyte – $2,37x10^3/\mu L$, monocyte – $1,8x10^3/\mu L$, eosinophils – $1,09x10^3/\mu L$, basophil – $0,03x10^3/\mu L$).
- oxygen saturation level - 100%
- general analysis of urine: relative density 1019 g/l, leukocytes - 16-20 in sight, fresh erythrocytes - 14-16 in the field of view, squamous epithelium - 8-10 in the field of view, bacteria, mucus in small quantities, single oxalates.
- biochemical and other studies: total protein - 66.9 g/l, alanine aminotransferase (ALT) – 48 UI/l, aspartate aminotransferase (AST) – 39 UI/l, alkaline phosphatase - 91.5 UI/l, antibody to streptolysin “O” (ASLO) – 139 IU/ml, RF - 7.93 UI/l, CRP - 38.2 mg/l, glycated haemoglobin - 5.7 mmol/l.

Instrumental examinations: ultrasound diagnosis - enlargement of mesenteric lymph nodes, X-ray diagnosis of chest organs, and echocardiography of the heart - no pathological changes were detected.

At the hospital, the patient was prescribed glucocorticosteroids (dexamethasone 16 mg/day), analgesics, proton pump inhibitors, pre-infusion therapy with electrolyte solutions, and local treatment of skin and mucous membranes.

As part of the research project, we performed total IgE and molecular genetic studies of herpesviruses (EBV, HHV6, CMV) and the antibiotic baseline test.

According to the results of the study - total IgE - 54.0 IU/l, EBV DNA, and DNA HHV6 "+" were detected in the saliva and mucous membrane of the posterior pharyngeal; CMV DNA was not detected in any biological media.

Figure.1. The photo of affection of the mucous membranes of the mouth and genitals in patient.

The phenotype of basophils presented in peripheral blood was analysed through two-colour flow cytometric analysis, based on Forward Scatter and Side Scatter parameters. BAT results in patient show in vitro changes in $CD63^+$ expression without stimulation (negative control) - 3.54%, stimulation positive control with anti-FcεRI Ab - PC1 - 80.86%, stimulation positive control with fMLP - PC2 - 38.48% (not shown) and the following antibiotic solutions: to clavulanic acid - 3.45% (within normal limits), amoxicillin (extended-spectrum penicillin) - 17.31%, to ceftriaxone (other beta-lactam antibiotics, cephalosporins of the third generation) - 8.94%, to cefuroxime (cephalosime) (cephalosporins) of the 2nd generation – 14.33% (Fig.2).

For further treatment of yersiniosis, the patient was referred to an infectious disease specialist with recommendations. We were asked to continue treatment with Doxacycline.

Discussion. In everyday clinical practice, the diagnosis of delayed-type allergic reactions is more severe than the immediate type, primarily due to the variety of pathogenetic variants of their formation. Clinical conditions are not always suitable for in vivo diagnostic tests; therefore, different methods of in vitro diagnosis of DHRs are relevant. One of the in vitro diagnostic tests is BAT [12]. The essence of BAT is to determine the expression of markers activation of $CD63^+$ on basophil membranes, which changes after stimulation with the studied drugs (in particular, various types of antibiotics) in vitro [13]. The data from investigators showed that BAT in the diagnosis of immediate-type reactions to beta-lactams, clavulanic acid, and other antibiotics demonstrates relatively high sensitivity (38-55%) and specificity (79-96%) [6]. In particular, in a recent study, BAT demonstrated high efficacy and prognostic value for clavulanic acid and was preferred in the diagnosis of DHRs to amoxicillin in the treatment of patients with suspected amoxicillin-clavulanic acid allergy [14]. BAT results are also used for drug desensitization in patients who require full therapeutic doses of vital drugs for treatment [15].

According to the study results, we did not observe changes in CD63+ expression in response to clavulanic acid stimulation but found a significant increase in its expression in response to amoxicillin (5.1 times), ceftriaxone (2.52 times), cefuroxime (4.15 times), which occurred after cross-linking of specific IgE associated with high affinity of FcεRI receptors. The patient described by us showed hypersensitivity on the 3rd day after taking BLA in the form of bullous manifestations of SJS, which refers to severe allergic reactions of delayed type. Confirmation of the allergic reaction was a positive BAT to amoxicillin - 17.31 and negative to clavulanic acid - 3.45, which is also part of Augmentin. Therefore, we can assume that in this case, BAT confirmed that the patient had a delayed allergic reaction to amoxicillin.

After processing a large amount of scientific data, we tried to understand the results and put forward our possible explanations.

The early science study suggested the use of BAT to diagnose and monitor patients with suspected chronic urticaria of autoimmune origin, which is characterized by heterogeneity in induction, and duration of exacerbations, and shows different mechanisms of formation. In particular, there was an increased ability to express activation markers of basophils $CD63^+$ and CD203c in patients with autoimmune thyroiditis, and the presence of IgE and IgG targeted towards thyroid peroxidase compared with healthy individuals [16,17]. Regarding systemic autoimmune pathology, the association of DHRs to antibiotics in the form of SJS in Sjogren's syndrome (SS), systemic lupus

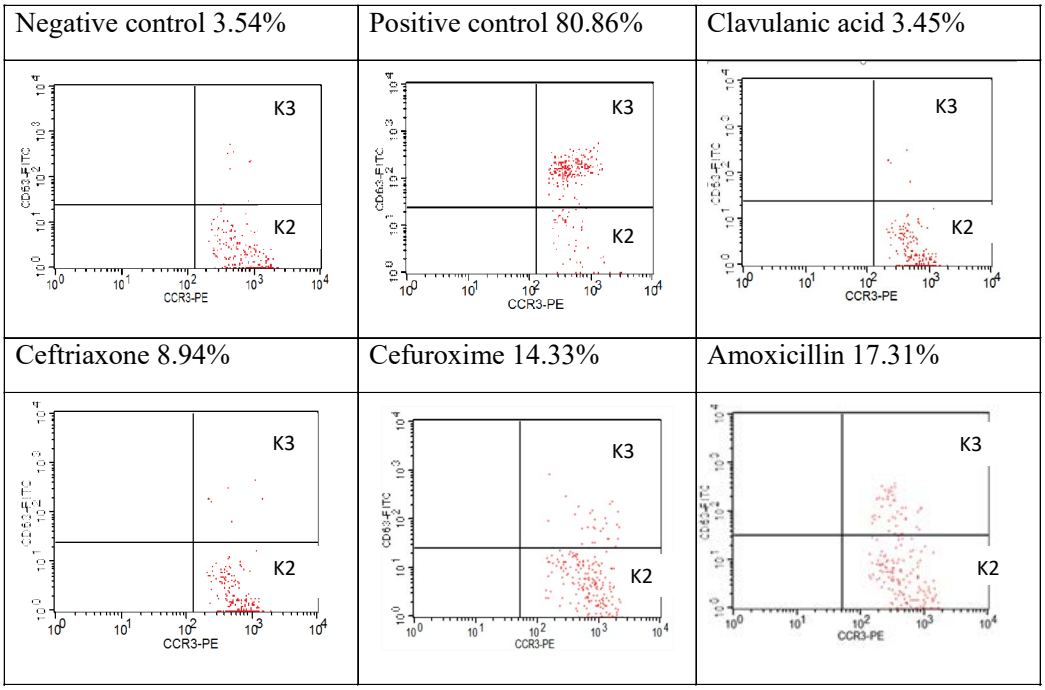

Figure. 2. Flow cytometry dot plots of basophils distribution: quadrant K2 - inactivated cells (CCR3+/CD63−), quadrant K3 - activated cells (CCR3+/CD63+). Fluorescence channels FL1 (CD63-FITC) and FL2 (CCR3-PE).

erythematosus (SLE), and rheumatoid arthritis (RA) has been most commonly described [18], in patients with neutrophilic inflammation.

In particular, the group of Wang et al. analysed six fatalities in patients with SJS that occurred after taking even small doses of antibiotics. Among all patients, the main disease was the autoimmune diseases mentioned above [19]. It is believed that the mechanisms involved in skin lesions and associated with the manifestation of SJS in autoimmune diseases include dysfunction of regulatory T cells (Tregs) and neutrophil extracellular traps (NETs) [20,21,22].

We may assume that our patient has already developed an autoimmune syndrome, as the anamnesis indicates arthralgia, chronic recurrent tonsillitis, low-grade fever, etc. This likely contributed to characteristic changes in the immunopathogenesis of DHRs (presence of inflammation markers, T-helper activation, and dysfunction of T-regulatory immune systems), which caused the formation of delayed-type reactions (cell-mediated) and formed the basis of positive BAT results. Therefore, the patient is scheduled for additional specific studies on autoimmune syndrome.

In our opinion, another explanation may be that the patient developed reactivation of herpes virus infections. It has been described that allergic reactions (DHRs) to drugs in the form of SJS / TEN with HHV-6 reactivation were more severe, accompanied by pronounced activation of the immune response, which was clinically manifested by visceral lesions [23,24].

A characteristic feature of the immune response to viral infection is the activation of antiviral cytotoxic mechanisms (NK cells, CTL, increased TNF-α concentration, etc.), and these factors may also contribute to rapid apoptosis and necrosis of keratinocytes and epithelial cells in SJS. An association between active HHV-6 infection and severe DRESS is also known [25]. The causal relationship between herpes virus reactivation and hepatotoxicity, as well as the risk of severe life-threatening events, were assessed. The authors proposed to make possible laboratory herpesviruses reactivation (primarily HHV-6) as risk factors for DHRs, taking into account the results for further treatment of the patient and prevention of severe drug reactions on the skin [26]. Other authors have described a similar clinical case in a patient receiving cyanamide, but in this case reactivation of not only HHV-6, but also HHV-7, CMV, and HSV ½ infections was found [27]. According to M. Seishima et al., the association of delayed-type DHRs with reactivation of HHV-6, -7, CMV, and/or EBV was revealed after exposure to certain drugs, including anticonvulsants [28].

Thus, in the numerous severe clinical cases of DHRs described, most authors confirmed the role of herpesviruses, HHV-6 in particular in the mechanisms of their formation. Therefore, it seems possible that in our case, with the reactivation of HHV-6 and EBV, combined with increased activity of liver enzymes, which we observed in this patient, these viruses could contribute to delayed-type of DHRs, confirmed by positive BAT results.

We also noted that our patient's BAT was positive for both ceftriaxone (other beta-lactam antibiotics, third generation cephalosporins) - 8.94%, and cefuroxime (second-generation cephalosporins) - 14.33% and negative for clavulanic acid - 3.45%.

It has been expressed a suggestion in the literature that the most important allergen in BLA is the ring structure which is common to all BLAs. Therefore, it was assumed that allergy to one substance in the BLA group meant cross-allergy to all other BLAs [29]. It was determined that BLA consists of allergenic components that differ from each other. Therefore, the probability of combinations of these cross-reactive fragments in the BLA structure is much higher. That is, most patients with hypersensitivity reactions to one of the BLAs should never avoid treatment with other BLAs.

Probable cross-reactions between different classes of BLA are clearly described in the Guideline on diagnostic procedures for suspected hypersensitivity to beta-lactam antibiotics [6]. In particular, it was determined that testing clavulanic acid as a single substance for test purposes showed greater sensitivity for the detection of clavulanic acid sensitization compared to testing solely with the finished medicinal product together with amoxicillin. After performing a separate study of BAT to clavulanic acid, we obtained a negative result, which ruled out the possibility of a hypersensitivity reaction to one of the components of the drug that the patient was taking. This is obviously due to other allergenic components that are involved in our case in cross-reactivity.

According to the special literature, there are cross-reactions between BLA and cephalosporins of the first and second generations and our patient proved it with a highly positive BAT to cefuroxime (cephalosporins of the II generation) - 14.33. In addition, we also received a positive BAT for ceftriaxone (third generation cephalosporins). As mentioned above, high cross-allergy between penicillin and cephalosporins was previously assumed based on the common beta-lactam ring. However, based on numerical clinical data, the relevant warnings have been refuted. Other cephalosporins, such as ceftriaxone, are thought to exhibit cross-reactivity with penicillins only in isolated cases. However, cross-reactivity should not be underestimated, as it causes severe systemic reactions and even fatalities [30].

In addition, the example of our study demonstrated the diagnostic value of using BAT to detect cross-reactions between different groups of beta-lactam antibiotics. Based on the results of BAT and the clinical picture of SJS, we recommended that the patient refrains from further use of cephalosporins in the second and third generations.

The study was conducted following the 7th revision of the principles of the Declaration of Helsinki Human Rights (2013), the Council of Europe Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. The Ethics Committee approved the study of Clinical Research at Danylo Halytsky Lviv National Medical University (protocol № 6 dated June 22, 2021). All procedures performed were by the ethical standards set by the institutional and national research committee. Informed consent was obtained from the patient before any study-related procedures were initiated. Based on the developed international positional documents and the unified clinical protocol “Drug allergy, including anaphylaxis”, in 2015

[31] the author's questionnaires were formed: information letter for primary care physicians and allergists, patient questionnaire cards, and patient examination card [32].

Conclusions. We have described a clinical case that shows that reactivation of HHV6 and EBV herpesviruses is a higher risk of allergic reaction to antibiotics. High indices of antibiotic stimulation (amoxicillin, ceftriaxone cefuroxime) of $CD63^+$ expression obtained by performing BAT on a patient make this test recommended for the diagnosis of delayed-type DHRs. BAT results showed the possibility of cross-reactions between penicillin and second-and third generation of cephalosporin, indicating the possibility of using this in vitro cell test to diagnose the risk of cross-reactions between antibiotics.

In the example of this clinical case, we have expressed our owns on new possibilities for the use of BAT. However, our project continues, and to confirm or refute our findings, we have planned to perform BAT on at least 20-30 patients with delayed types to BLA.

Conflict of interest. The authors have no conflict of interests to disclose.

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