Original paper

Acute urticaria in children: course of the disease, features of skin microbiome

Ekaterina Orlova, Lyudmila Smirnova, Yuri Nesvizhsky, Dmitrii Kosenkov, Elena Zykova

Department of Dermatology and Venereology, I. M. Sechenov First Moscow State Medical University, Sechenov University, Moscow, Russia

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Abstract

Introduction: Quantitative and qualitative changes in the microbiome of the skin affect the emergence and course of allergic diseases, in particular, of acute urticaria.

Aim: To investigate the taxonomic composition of the skin microbiota in children with acute urticaria and to study its effect on the course of the disease.

Material and methods: In total, 75 children with diagnosed acute urticaria at the age of 7–-14 years were examined. The average age of children was 10.83 ±0.95, of which 44 (58.7%) were boys, and 31 (41.3%) were girls. The control group consisted of 30 virtually healthy children of the appropriate age, of whom 16 (53.3%) were boys, and 13 (46.7%) were girls.

Results: Regardless of the severity of the disease, the examined children suffering from acute urticaria had sensitization in history with a significant prevalence of food sensitization ($p < 0.05$). The occurrence of a severe episode of acute urticaria is associated with allergens of drug origin in 52.6% of cases and the action of unidentified triggers in 47.4% of cases. In children with acute urticaria, *S. epidermidis*, *S. aureus*, bacteria of the genus *Peptococcus*, and *Peptostreptococcus* dominated on a non-affected skin area, while for the affected skin area, the *Propionibacterium*, *S. aureus*, *S. epidermidis*, bacteria of the genus *Peptococcus*, *Propionibacterium*, and *Peptostreptococcus* were denoted as dominating.

Conclusions: High frequency of *S. aureus* detection on affected and non- affected skin areas in children with acute urticaria is a predictor of the disease severity.

Key words: acute urticaria in children, features of acute urticaria, sensitization and acute urticaria, skin microbiota and urticaria.

Introduction

Children's allergic diseases (AD) are quite a sensitive problem for modern medicine and the global health system being the reason for significant socio-economic expenses due to their high prevalence, which has increased dramatically in recent years [1]. The ADs have a negative impact on quality of life, increasing the frequency of concomitant pathology and the risk of death, such as in bronchial asthma [2]. Negative economic consequences of AD are associated with significant direct (visit to a doctor, hospitalization, intensive care unit treatment, laboratory and instrumental diagnostics, conservative treatment, etc.) and indirect medical expenses (work and study absences, resulting in lower production volumes, worse productivity, and poor performance) [3]. The prevalence of AD is quite difficult to study due to its difference within the country depending on the region, which is explained by the interaction of genetic and environmental factors [1]. Allergic diseases include several genetically heterogeneous and immunologically determined diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis, food allergies, and acute urticaria (hives). Almost 700 million people worldwide suffer from respiratory ADs alone (bronchial asthma and allergic rhinitis) [4–6].

For many years, acute urticaria (AU) has been considered as nearly the most relevant problem in allergology, especially among children [7, 8]. The peak of morbidity of this pathology in children occurs in the age period from 14 to 16 years, although, over the last 5 years, a tendency

Address for correspondence: Ekaterina Orlova, Department of Dermatology and Venereology, I. M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia, phone: +79036181553, e-mail: orlovaeka995@rambler.ru
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to higher morbidity is denoted among children of preschool and primary school age. In general, the prevalence of AU among children is 2.1–6.7% (in Great Britain – 3.4%, in Germany – 4.4%, and in Denmark – 5.4%), and among children with atopic dermatitis, the incidence rate is higher and amounts to about 16.2%. This disease was observed at least once in 10–20% of children, and in 5.4% of cases, it was diagnosed in preschool-aged children [8]. Besides, more than half of the children with AU are diagnosed with other allergic pathologies as well [9].

Infective agents, food, and medicines are among the main trigger factors for AU in children [10–12]. Acute spontaneous urticaria occurs in preschool children with atopy. Infection in children is probably the most common predictor of AU compared to adults, with infection being the most frequently documented cause of this allergic pathology in children (about 40% of cases) [12, 13]. Infectious agents associated with the emergence of AU include viral (rotavirus, rhinoviruses, herpes simplex virus, Epstein-Barr, hepatitis A, B, and C, and human immunodeficiency virus), bacterial (streptococcus, mycoplasma, Helicobacter pylori), and parasitic agents (protozoa, helminths). Aspirin and other non-steroidal anti-inflammatory drugs, β-lactam antibiotics, vancomycin, and opiates are the drugs most often associated with the occurrence of AU and cause the disease through direct degradation of mast cells. In most cases, the cause of acute urticaria is possible to establish [13].

The pathogenesis of AU is based on allergic reactions of immediate type, i.e., type I, less often type II and III. In such allergic reactions, allergens interact with specific antibodies-reagents of basophilic membranes and adipose cells, resulting in degranulation of these cells with the release of biologically active substances that cause typical symptoms of the disease. In particular, histamine is associated with itching, oedema, and hyperaemia on the periphery of the bladder. Histamine, cytokines, platelet activation factor incites the expansion of blood capillaries, plasma sweating, and also the migration of macrophages, neutrophils, T-lymphocytes in the area of the urticant lesion. Other mediators affecting the development of AU include prostaglandin D2, calcitonin binding peptide, substance P, and eicosanoids [8, 9]. Non-immune mechanisms of AU are much rarer and arise as a result of 1) an increase in the concentration of histamine due to its non-specific release from mast cells by the non-immune way, for example, at eating or taking some medicines; increase in the concentration of this mediator through inhibition of the enzyme activity of diamine oxidase, which directly participates in its destruction; as a result of its oversupply with certain foods (smoked food, cheeses, tuna, cod, chocolate, nuts, spinach, avocado, tomatoes, beer) and its increased synthesis in the body (e.g., in intestinal dysbiosis); 2) arachidonic acid metabolism disorders as a result of non-steroidal anti-inflammatory drug intake; 3) excessive acetylcholine secretion due to physical and psycho-emotional exhaustion or high-temperature action; 4) complement system activation when injecting X-ray-contrast substances); and 5) bradykinin accumulation in blood, when angiotensin-converting enzyme inhibitors are taken) [8, 9, 14].

The AU is manifested by the sudden appearance of wheals, which is associated with the influence of the trigger factor, and the duration of this condition is less than 6 weeks. Wheals do not have a certain typical localization, are accompanied by itching, and can merge in places of close contact with clothes [15]. The wheal is oedema of one of the skin layers – dermis, has a limited character, and usually disappears in 24 h. Its diameter varies from a few millimetres to several centimetres, and it is characterized by intense hyperaemia of the peripheral part and swelling of the central part. Sometimes the pathological process may extend to deeper layers of the dermis and subcutaneous adipose tissue or mucous membranes resulting in the formation of angioedema, or Quincke's oedema, for which painfulness and a longer regression of up to 72 h are typical. Isolated form of hives in the form of urticaria is found in 40% of cases, the Quincke's oedema in 11% of cases [16], and the combination of urticaria and Quincke's oedema is revealed in 49% of cases [13]. Besides the local skin manifestations, children with oedema may experience increases in body temperature to febrile values, dyspepsia, abdominal and joint pain, which may lead to erroneous hospitalization in an infectious hospital [17].

The AU is diagnosed based on the clinical symptomatology of the disease, namely the presence of the typical urticanthropic hives described above, as well as anamnesis data relationship of its occurrence to the action of a certain agent [15]. Usually, it is sufficient for diagnosis of AU, and there is no necessity to perform additional routine laboratory examinations. Only in case of suspicion of drug hypersensitivity or IgE-dependent mechanism of food intolerance, it is required to admit the child to the allergologist's consultation for allergy diagnostics [13, 15].

Treatment tactics for AU should be aimed primarily at the elimination of the triggering agent from the child's body. Of great importance is the therapeutic nutrition excluding food referred to as histamine liberators [13, 15]. Medicines of the first line include antihistamines (non-sedative), and glucocorticosteroids are recommended in case of their ineffectiveness. Noteworthy is that for symptomatic treatment of AU in children, it is allowed and recommended to use only drugs with reliable evidence, which have proven clinical efficacy [13, 15, 17].

Considering the increasing prevalence of allergic diseases among children, including AU, the issue of studying and revealing new pathogenetic links of their origin and progression is of current importance as it can improve the diagnostic algorithm and increase the efficiency of

treatment of allergic conditions. In particular, the study of the influence of the skin microbiome on the emergence and course of AU has attracted the special attention of scientists in recent years [18–20]. Such interest in the skin microbiome is due to its extreme diversity (enrolling about 1014 taxonomic units) and absolutely unique ecosystem, the peculiarities of which depend on sex, comorbid pathology, environmental factors, a region of residence, etc. [20]. The growth of *Streptococcus* and/or *Propionibacterium* ratio in the skin microbiome was established to correlate with the appearance of atopic dermatitis, while some *Acinetobacter* species, in contrast, protect the skin from allergic sensitization and inflammation and participate in maintaining the balance of Th1 and Th2 [4, 19]. The studies proved the *Staphylococcus aureus, Escherichia coli, Helicobacter pylori,* and *Pseudomonas aeruginosa* to be capable of releasing histamine from the reserves of the human body, while some taxon representatives of *Acinetobacter, Serratia, Pseudomonas, Staphylococcus, Corynebacterium,* and *Micrococcus* demonstrate histidine decarboxylating effect, which indicates that quantitative and qualitative changes of skin microbiome influence the appearance and flow of AU [21]. However, very few studies have been performed on this issue, and most of them have examined the influence of skin microbiota on the origin and course of atopic dermatitis [22, 23]. The lack of sufficient data on acute urticaria (hives) specifies the necessity of further research on this issue.

Aim

The study aimed to examine the taxonomic composition of the skin microbiota in children with acute urticaria and study its effect on the course of the mentioned disease.

Material and methods

A total of 75 children at the age of 7–14 years with the diagnosis of acute urticaria were examined. The average age of children was 10.83 ±0.95, of which 44 (58.7%) were boys, and 31 (41.3%) were girls. The control group consisted of 30 virtually healthy children (VHC) of the appropriate age, of whom 16 (53.3%) were boys, and 13 (46.7%) were girls. Surveys were conducted between 2017 and 2019, and the number of children in this age group was 16 (53.3%) boys and 13 (46.7%) girls. The disease was verified following the recommendations of the European Academy of Allergology and Clinical Immunology, the European Global Allergy and Bronchial Asthma Network, the European Dermatological Forum and the World Allergy Organization (The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria) [15].

All studies were conducted in compliance with the Convention of European Council "On Human Rights and Biomedicine" (04.04.1997), the Helsinki Declaration of the World Medical Association "On Ethical Principles for Medical Research involving Human Subjects" (1964–2013), and ICH Good Clinical Practice (1996).

The study included children who met the following criteria: age from 7 to 14 years, verified diagnosis of acute urticaria, voluntary informed consent to participate in the study signed by the child's parents or legal guardian.

Children, who had at least one of the following criteria, were not included in the study: age under 7 years and over 14 years, concomitant dermatological disease, history of an infectious disease suffered earlier than a month before being included in the study, intestinal infection within the last 3 months, antibiotic therapy within the last 3 months, presence of other pathology of internal organs in the acute stage, oncopathology, and mental disorders.

The level of AU severity was assessed with 0 to 3 points considering such parameters as the number of morphological elements of the rash, duration of the rash, and severity of itching. With a total score of ≤ 3, the course of AU was assessed as mild, AU with 4–6 scores as moderate, and with ≥ 7 scores as severe [24].

The study of the skin microbiome in VHC was performed on the middle third of the forearm (on its inner surface), and in children with AU – on the affected area of the skin and on a non-affected surface symmetrical to the affected one. The material for the bacteriological study was extracted through a bacterial seal (Murray PR2015). Extracted material was sown within 1 h to nutrient and differential-diagnostic media produced by HiMedia Laboratories Pvt. Ltd, India, namely, HiGrome Aureus Agar Base, Endo Agar, HiGrome Enterococci Agar, HiGrome Candida Differential Agar, Blood Agar Base – for facultative anaerobic bacteria, Schaedler Agar, Bacteroides Bile Esculinum Agar, and Anaerobic Agar – for non-clostridial anaerobic bacteria. After 24 h of incubation in a thermostat at 37°C, the grown pathogenic colonies of microorganisms were identified by examining their morphology, tinctorial features, and biochemical properties.

Statistical analysis

The Student *T*-criterion and Wilcoxon non-parametric *T*-criterion were applied for statistical analysis. The differences were considered statistically significant at $p < 0.05$. The χ^2 criterion was used to numerically interpret the qualitative features and compare the detection rates of individual skin microorganisms. All statistical operations were performed using Statistica for Windows 10 Pro (Stat Soft Inc., USA) and Microsoft Excel 2013 (Microsoft, USA) software packages.

Results

While studying the anamnesis, the food products were established as the main cause of AU development in 34 (45.3%) children, then medicines – in 22 (29.4%) children, and other factors, such as plant pollen, contact allergens, etc., in 7 (9.3%) children. At that, for 12 (16%) children, no triggering factor for AU has been detected. Noteworthy is that the majority of children with acute urticaria had an aggravated allergic history, i.e., 68 (90.7%) children, of whom 46 (61.3%) children had a history of food allergy, 29 (38.7%) children had drug intolerance, 19 (25.3%) children had atopic dermatitis, 8 (11.7%) children had allergic rhinitis, and 6 (8%) children suffered from bronchial asthma.

In considering the specifics of the disease flow, 18 (24%) children under examination were diagnosed with the mild form of AU, 38 (50.7%) children had moderate AU, 19 (25.3%) children had severe AU. The incidence rate of moderate flow of the disease was significantly higher in comparison with the mild ($p < 0.05$) and severe ($p < 0.05$) forms of acute urticaria. No statistically significant differences in the severity of the disease between girls and boys were recorded ($p > 0.05$).

In children with a mild form, the main cause of the disease was food allergens determined in 8 (44.4%) children, then pollen and contact allergens – in 7 (38.9%) children, significantly less often ($p < 0.05$) compared to the triggers mentioned above. The cause of the mild OK episode was medicines – only in 3 (16.7%) children. For all children with mild AU, the triggering factor for the episode was possible to establish.

For moderate severity, the occurrence of the AU episode in most cases was associated with food allergens in 18 (47.4%) children, medications in 13 (34.2%) children, and undefined allergens in 7 (18.4%) children.

All (100%) children with severe AU had allergic anamnesis, while in the past, sensitization with food products prevailed significantly more often ($p < 0.05$) – in 9 (47.4%) children. The development of severe AU episodes in the examined children was mainly related to allergens of medication origin, namely, in 10 (52.6%) children, which is significantly more frequent than with a mild form ($p < 0.05$). The influence of unidentified triggering agents was noted in 9 (47.4%) children, which is significantly more frequent than with mild ($p < 0.05$) and moderate ($p < 0.05$) degrees of severity. Severe AU in response to food allergens was not recorded in the study performed.

In addition to the main skin manifestations of AU in the children included in the study, concomitant symptoms, such as general weakness, headaches, discomfort/abdominal pain, nausea, single vomiting, and stool disorders, were also observed. Most commonly children complained of general weakness, headaches, and nausea. In children with severe disease, concomitant symptoms were reported in 100% of cases, which is significantly more frequent ($p < 0.05$) compared to moderate (concomitant symptoms were present in 24 (68.4%) children) and mild symptoms (concomitant symptoms were present in 7 (38.9%) children).

During the study of the species composition of skin microbiota, 11 species of microorganisms (7 facultative anaerobic (FA) and 5 non-clostridial anaerobic (NCA)) were detected in VHD and 12 species (6 FAs and 6 NCAs) were found in children with AU. The average bacteria insemination of the skin by FAs in VHD were 2.3 ±1.2 CFU/sm^2, by NCAs – 1.9 ±0.8 CFU/sm^2. The average bacteria insemination of the healthy skin by FAs in children with AU were 3.3 ±1.7 CFU/sm^2, by NCAs – 1.6 ±0.5 CFU/sm^2, and that of the injured skin by FAs – 3.0 ±1.6 CFU/sm^2, by NCAs – 1.6 ±0.6 CFU/sm^2. Among FAs, *S. epidermidis* was more frequently detected in 28 virtually healthy children (93.3%), *Micrococcus* genus microorganisms in 18 (60%) children (Figure 1), *Peptococcus* bacteria in 13 (43.3%) children, and *Peptostreptococcus in* 9 (30%)

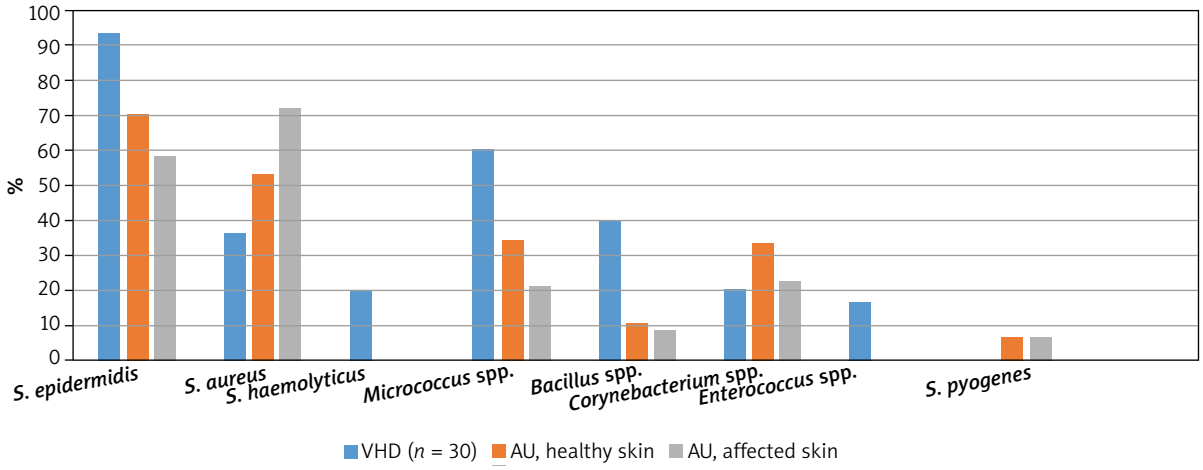

Figure 1. Emergence frequency of facultative anaerobic skin microbiotic taxons in children with acute urticaria (AU), %

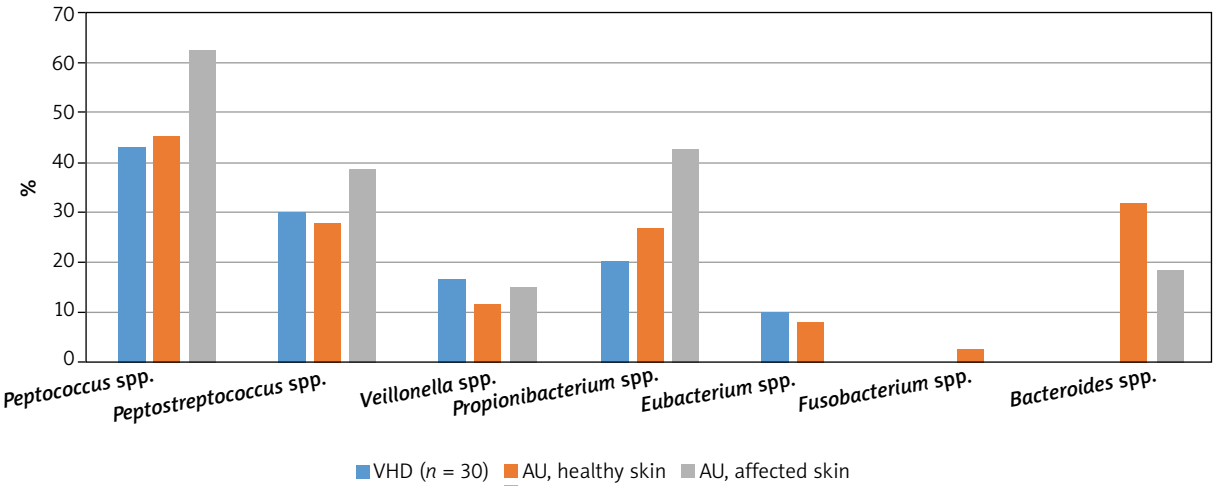

Figure 2. Emergence frequency of clostridial-anaerobic skin microbiota taxons in children with acute urticaria (AU), %

children (Figure 2). In children with AU on a non-affected skin area, *S. epidermidis* dominated in 53 (70.7%) children, *S. aureus* was found in 40 (53.3%) children (Figure 1), *Peptococcus* bacteria was present in 34 (45.3%) children, *Peptostreptococcus* was visible in 21 (27%) children, and *Propionibacterium* was revealed in 20 (26.7%) children (Figure 2). Those with confirmed AU in the affected skin area, *S. aureus* dominated in 54 (72%) children and *S. epidermidis* – in 44 (58.7%) children (Figure 1). Among the NSAs, *Peptococcus* bacteria prevailed in 47 (62.7%) children, *Propionibacterium* – in 32 (42.7%) children, and *Peptostreptococcus* – in 29 (38.7%) children (Figure 2). Thus, in children with AU, *S. aureus* was detected 1.96 times more frequently ($p < 0.05$) in the affected skin area as compared to VHD, and 1.45 times more frequently ($p < 0.05$) in the non-affected skin area as compared to the non-affected skin area at AU. *S. epidermidis* in children with AU was detected 1.3 times ($p < 0.05$) less frequently in the non-affected skin area compared to VHD, while in the affected area – 1.6 times ($p < 0.05$) less frequently. Bacteria of genus *Micrococcus* were recorded 1.7 times ($p < 0.05$) and 2.8 times ($p < 0.05$) less frequently and that of genus *Bacillus* – 4.3 times ($p < 0.05$) and 3.7 times ($p < 0.05$) less frequently in the non-affected and affected skin area, respectively. Representatives of the genus *Propionibacterium* were 2.1 times ($p < 0.05$) more frequently detected on the affected skin area of children with AU compared to VHD and 1.6 times ($p < 0.05$) more often on the affected skin area at AU compared to healthy areas.

The *Streptococcus pyogenes* was found in 5 (6.7%) children ($p < 0.05$) with AU compared to VHD, as well as *Bacteroides* was detected in 14 (18.7%) children ($p < 0.05$) with AU in the affected area of skin and 24 (32%) children ($p < 0.05$) with AU in a healthy skin area compared to VHD. In contrast, 6 (20%) virtually healthy children ($p < 0.05$) had *Staphylococcus haemolyticus* in the skin microbiome and 5 (16.7%) children ($p < 0.05$) had *Enterococcus* genus, which was not recorded among children with acute urticaria.

The study of emergence frequency of certain microbiota taxons on the affected and non-affected areas of the skin of children with AU depending on the severity of the disease has shown that in case of the moderate AU, bacteria of genus *Bacteroides* ($p < 0.05$) were detected on the affected area of the skin significantly more frequently in comparison with VHD against the background of the decrease of *Bacillus* bacteria incidence ($p < 0.05$). In the case of the severe form of the disease, the *S. aureus* bacteria ($p < 0.05$) was noticed significantly more frequently. On non-affected skin areas in children with mild AU in comparison with VHD, the bacteria of genus *Propionibacterium* ($p < 0.05$) were detected significantly more often, for the medium form, bacteria of genus *Bacteroides* ($p < 0.05$) prevailed, and for severe forms – *S. aureus* ($p < 0.05$). Besides, the emergence frequency of bacteria of genus *Micrococcus* ($p < 0.05$) decreased significantly in the case of a severe form of the disease.

Discussion

When studying the anamnesis and course of AU in children it has been established that in 90.7% of children, a burdened allergic anamnesis for both mild and severe course of the studied disease was observed. In general, among triggering agents of AU episodes development in this study, food sensitization significantly prevailed accounting for 61.3% ($p < 0.05$) of cases. At the same time, the development of a severe episode of this disease was associated with sensitization by drugs ($p < 0.05$) and unidentified triggering allergens ($p < 0.05$). Concomitant symptoms, such as general weakness, headache, nausea, vomiting, abdominal pain/discomfort, and stool disorders, were significantly more typical of the severe form

(100% of cases at $p < 0.05$) compared to the moderate (68.4%) and mild (38.9%) forms.

When examining the composition of the skin microbiota in AU children, a significant increase in the frequency of *S. aureus* detection ($p < 0.05$) both on the affected and non-affected skin areas was recorded compared to virtually healthy children. Besides, the emergence frequency of this microorganism increased with greater severity of the disease. It allows asserting that a higher incidence of *S. aureus* in children with AU is a predictor of the severity of this nosology.

Typical was also a significant reduction in the incidence rate of *S. epidermidis* ($p < 0.05$) in children with AU, which is the most common microorganism on the skin of a healthy person. *S. epidermidis,* together with other coagulase-negative staphylococci, can release antimicrobial agents that inhibit the growth and formation of *S. aureus* biofilm [21]. In addition to changes in the emergence frequency of these species of *staphylococcus*, the variations in the incidence frequency of other skin microbiome species (genus *Micrococcus, Corynebacterium, Bacillus, Propionibacterium*) has been revealed, which indicates the presence of complex relationships between different taxons of skin microbiota and the need for their comprehensive and detailed study. The production of *S. epidermidis* and *S. aureus* antimicrobial substances (bacteriocins, antimicrobial peptides) incites a decrease in the relative number of *Micrococcus, Bacillus,* and *S. haemolyticus* bacteria during the AU episode [23, 25].

The data obtained concerning the main triggering factors of AU episodes development and its flow features are generally comparable with the results of other similar studies [17, 24]. However, more research in the literature is devoted to the study of skin microbiome features in atopic dermatitis enrolling both adults and children [22, 26]. In particular, a study involving 128 people aged 2–62 years revealed the predominance of healthy individuals of the bacteria of genera *Staphylococcus*, *Propionibacterium, Corynebacterium,* and *Streptococcus* on the skin microflora*,* and*, S. aureus, Propionibacterium, and Peptococcus* on the skin of patients with atopic dermatitis [26], which is consistent with the results of this research. A similar study was conducted in Russia with 61 AU children at the age of 3–12 years. It has been established that the severe flow of AU is associated with medication sensitization and increased frequency of *S. aureus* detection on the affected skin area in AU children [24], which also corresponds to results of this study.

Conclusions

Thus, the results obtained in this study showed that, regardless of the severity of the acute urticaria flow, the surveyed children suffering from this disease had sensitization in their history, namely, 61.3% of children – food allergy, 38.7% – medication intolerance, 25.3% – atopic dermatitis, 11.7% – allergic rhinitis, and 8% – bronchial asthma. At that, food sensitization prevailed ($p < 0.05$). The occurrence of a severe episode of acute urticaria is associated with allergens of medication origin (in 52.6% of cases) and the action of unidentified triggers (in 47.4% of cases), which is significantly more frequent in comparison with a mild form of the disease ($p < 0.05$). In children with acute urticaria, S. *epidermidis* dominated in a non-affected skin area (in 70.7% of cases), while *S. epidermidis. S. aureus* (in 53.3%), bacteria of the genus *Peptococcus* (in 45.3%), *Peptostreptococcus* (in 27%), *Propionibacterium* (in 26.7%), *S. aureus* (in 72%), *S. epidermidis* (in 58.7%), bacteria of the genus *Peptococcus* (in 62.7%), *Propionibacterium* (in 42.7%) and *Peptostreptococcus* (in 38.7%) prevailed on the affected area. In children with AU, *S. aureus* was detected 1.96 times more frequently ($p < 0.05$) in the affected skin area as compared to VHD, and 1.45 times more frequently ($p < 0.05$) in the non-affected skin area as compared to the non-affected skin area at AU. *S. epidermidis* in children with AU was detected 1.3 times ($p < 0.05$) less frequently in the non-affected skin area compared to VHD, while in the affected area – 1.6 times ($p < 0.05$) less frequently. High frequency of *S. aureus* detection on the affected and non-affected skin areas in children suffering from acute urticaria can be considered as a predictor of the disease severity.

Prospects for further research: a prospect for further research is to examine the efficacy of probiotic use in children with severe and severe acute hives.

Conflict of interest

The authors declare no conflict of interest.

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