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# Modern approaches to pathogenetic treatment of chronic urticaria

**Key words:** *rash, pruritus, urticaria, histamine, disbiosis, intestinal tract.*

Urticaria is one of the most difficult problems of modern allergology. This is due to the high prevalence rate of this pathology, mainly in active working age, with a high incidence of idiopathic forms (for acute urticaria 50 %, for chronic urticaria - 95 %), a frank decrease in the life quality of patients and frequent failure of diagnostic and remedial measures.

Urticaria – is a common disease characterized by appearance of pruriginous wheals on the skin. The wheal is formed as a result of papillary dermis hydrops and has the next defining characteristics: is an unstriped element, rises above the skin surface, turns pale when pressed and passes away traceless during the day.

Chronic urticaria affects the general health and everyday life of patients. The main complaint of patients with chronic urticaria is pruritus that is significantly frank in most patients (82 %). Every fourth patient has a sleep disturbance because of pruritus. Persistent symptoms of chronic urticaria are reflected on the psychological well-being of patients, particularly those with long-term course of the disease. Patients are suffering a constant internal stress due to the unpredictable nature of exacerbations.

Thus, chronic urticaria appears to be an important medical and social problem taking into account the high prevalence and long-term course of the disease, active working age of patients and a significant reduction in their quality of life.

In most patients the cause of chronic urticaria remains unknown. According to various authors proportion of chronic and idiopathic urticaria accounts for 80-95 %. However combination of chronic urticaria with certain chronic diseases is well known.

Chronic urticaria in the setting of gastrointestinal diseases (GID) was described by Hippocrates. So it is therefore extremely important to examine patients with chronic urticaria for gastrointestinal pathology (fibrogastroduodenoscopy, seeding feces for detection of intestinal dysbiosis). This examination method is extremely important, because with

intestinal dysbiosis the histaminase (inactivating histamine enzyme) generating process is interrupted.

Histamine is a key mediator in the urticaria pathogenesis as evidenced by:

- reproduction of urticarial rash with intradermal histamine release;
- Local release of histamine in the skin in patients with urticaria;
- Clinical efficacy of antihistamines.

Skin reaction to histamine is characterized by a Lewis triad: pruritus, wheal, reflex hyperemia, but the effectiveness of antihistamines is preferably 75 %. Therefore it is extremely important to find a complex of remedial measures that allow completely to relieve the symptoms of chronic urticaria and improve the life quality of patients.

In view of the above the purpose of the present study was to examine the effectiveness of a therapeutic complex that includes antihistamines, antileukotriene agents and dietary supplements.

## Materials and methods.

We observed 44 patients with chronic urticaria, aged from 18 to 65 years (mean age  $46,1 \pm 2,0$  years), 13 (29.5 %) of them were men and 31 (70.5 %) - women.

The study design was conducted in parallel groups. All patients were randomised into three clinical groups according to treatment regimens:

Group I (basic) - 16 patients were treated with last generation antihistamines (desloratadine in dosage 5 mg 1 tablet in the morning), montelukast sodium 10 mg 1 tablet in the evening (antileukotriene agent), Bionorm 1 tablet 2 times per day.

Group II (basic) - 16 patients were treated with H1-blockers and montelukast sodium in the same way, the agent-probiotic containing *Lactobacillus reuteri* Protectis - 1 tablec 2 times per day.

Group III (control) - 12 patients who received only a combination of antihistamines and antileukotriene agents. The duration of treatment was 3 weeks.

All groups were comparable in age and sex of patients ( $p > 0,05$ ).

Product Bionorm that was appointed to the patients of first group appeared to be a combination of activated lignin, lactulose and cellulose microcrystalline. Bionorm – is an original combination (which has no analogues) of 2 types of dietary fibers and lactulose with severe prebiotic and sorption effect to optimize the functioning of intestinal tract. Sorption strength is in 10-20 times greater than conventional adsorbents have (based on activated carbon). It operates in a complex, combining sorption and prebiotic effect, without damaging the intestinal tract. Lignin, having extremely high sorption capacity, fixes various microorganisms, their metabolic products, toxins of exogenous and endogenous nature, allergens, xenobiotics, heavy metals, radioactive isotopes, ammonia, divalent cations and promotes their excretion through the gastrointestinal tract. It also compensates the lack of natural dietary fiber (especially prebiotic) in the diet; optimizes the composition of the the large intestine microflora; normalizes nonspecific immunity.

Microcrystalline cellulose adsorbs on their surface and removes from the the body heavy metals, free radicals, microbial toxins, tissue decomposition products, and also fixes bile acids in the intestinal tract, bilirubin, cholesterol, stimulating their elimination.

Lactulose leads to excessive excretion of bile acids in the feces and, as a result, to enhanced formation of them in the liver from cholesterol. It also inhibits the production and absorption of ammonia and provides its rapid excretion in the feces.

Prebiotic agent tablet (group II) contains at least 100 teleorganic bacteria *Lactobacillus reuteri* Protectis, which increase the natural defense of the digestive system, create favorable conditions for the formation of the normal intestinal microbiocenosis, have immunostimulatory effects.

For all patients the histamine level in the blood plasma has been determined in the laboratory VIC-MEDIK (license of Ministry of Health Care of Ukraine АГ number 602777 from 04.08.2011) with the immunoenzymometric method of histamine determination in EDTA plasma (Elisa).

Assessment of intensity of the main clinical symptoms of urticaria (pruritus, rash) was carried out on a daily basis throughout the full therapeutical course in points: 0 - no

symptom, 1 – mild pronounced, 2 – moderate pronounced, 3 - strongly pronounced.

Intestinal tract dysbiosis has been determined with the bacteriological method.

Statistical analysis of the research results has been carried out using the software package Statistica v6.1®. Data are presented as the number of observations (n), the arithmetic mean and its standard error ( $M \pm m$ ), median (Me), 95 % confidence interval (95 % CI), the level of statistical significance (p), the Spearman correlation coefficient (r). For comparison of the average statistical characteristics in dynamics and in different observation groups Student's t test (for dependent and independent samples), Wilcoxon test, Mann-Whitney test, including the Bonferroni correction for multiple comparison and McNemar and Pearson Chi-square ( $\chi^2$ ) tests for comparison indexes were used.

## Results and Discussion

Dynamics of histamine level in the blood plasma in patients of all clinical groups is presented in Table 1.

As can be seen from the table, a significant ( $p < 0.001$ ) reduction of histamine in serum was noted in the main patients groups who were treated with combination of H1-blocker and antileukotriene agents with dietary supplement Bionorm or probiotic preparation. In the control group decrease in production of histamine was not significant ( $p > 0.05$ ).

Comparative analysis of the effect of different treatment regimens on the dynamics of the histamine level in serum of patients with chronic urticaria has showed a high degree of correlation ( $r = 0,68$ ;  $p < 0.001$ ) between the decrease rate of histamine production after treatment with a complex of therapeutic interventions (including the therapy with BAA (biologically active additives)). When statistically comparable baseline levels of the neurotransmitter in patients of all groups ( $p > 0.05$ ) in 3 weeks after completion of therapy, the differences between the main group I and control group have become statistically significant with  $p < 0.05$  (Fig. 1).

Under the influence of the treatment histamine production was normalized in 14 (87.5 %) and 9 (56.3 %) patients of the main groups and in 5 (41.7 %) patients in the control group. In the group of patients with chronic urticaria who were treated with probiotic agent, on completion of the therapeutic course differences in the average histamine levels in blood in comparison with the control group and the main group I have become the trend ( $p < 0,10$ ).

**Histamine level dynamics (ng / mL) under the influence of various treatment methods**

**Table 1**

Group	The observation period ( $M \pm m$ )		Dynamics	
	before treatment	after treatment	D	p*
Main group I (n=16)	2,21±0,24	0,56±0,08	-74,7 %	< 0,001
Main group II (n=16)	2,61±0,30	0,98±0,19	-62,5 %	< 0,001
Control group (n=12)	1,70±0,31	1,62±0,33	-4,7 %	> 0,05

Note. \* - Significant difference of indexes in the group by Student's t test for dependent samples

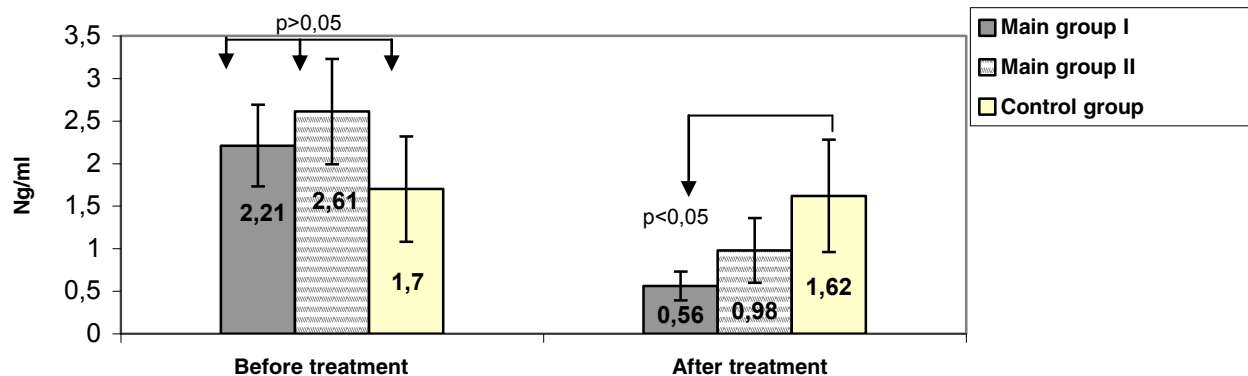


Fig. 1. Dynamics of average level (M, 95 % CI) of histamine in serum of patients with chronic urticaria for different treatment regimens: p - the level of significance of differences by Student's test with Bonferroni correction.

Analysis of the therapeutical effectiveness of intestinal dysbiosis in patients with chronic urticaria (Table. 2) has showed a significant improvement of the intestinal microflora in the main group of patients ( $p < 0.01$ ). Normalization of qualitative and quantitative composition of microflora was observed in 13 (81.3 %) patients treated with Bionorm and in 11 (68.8 %) patients treated with the probiotic. Intestinal dysbiosis has remained in the majority of patients in the control group (75.0 %). Dependence of the results of treatment of intestinal dysbiosis from the treatment regimens has been confirmed also with correlation analysis data -  $r = 0,44$  ( $P < 0.01$ ). In this case, the best results were observed in patients who have been treated with Bionorm.

The results has shown showed that normalization of histamine production in the blood plasma and the restoration of intestinal microflora in patients with chronic urticaria in case

of adding to treatment complex Bionorm agent and probiotic product leads to a significant improvement of the main clinical symptoms of the disease (Table. 3, Fig. 2, Fig. 3).

The best dynamics of clinical parameters was observed in the main group I when adding Bionorm agent, where all patients before treatment had strongly expressed pruritus and rashes ( $Me = 3$  points). During the first week of therapy intensity of symptoms was significantly reduced to 2 points ( $p < 0,001$ ), after 2 weeks – to 1 point ( $p < 0,001$ ), and after the end of treatment only the one patient has complained of a little itchy.

In patients of main group II who have received the probiotic agent containing *Lactobacillus reuteri* Protectis the severity of clinical symptoms was significantly decreased after 10 days of treatment ( $p < 0,01$ ), reaching the complete disappearance of rash in 11 (68.8 %) patients, pruritus – in 5 (31.2 %) to the end of treatment.

Table 2  
Dynamics in the number of patients with chronic urticaria with diagnosed intestinal dysbiosis under the influence of various treatment methods.

Group	The observation period (abs., %)		p*
	before treatment	after treatment	
Main group I (n=16)	16 (100,0 %)	3 (18,7 %)	< 0,001
Main group II (n=16)	15 (93,8 %)	5 (31,2 %)	< 0,01
Control group (n=12)	11 (91,7 %)	9 (75,0 %)	> 0,05

Note. \* - Significant difference in the group by the McNemar test

Table 3  
Dynamics of the intensity of the clinical symptoms in points (M ± m, Me) under the influence of various treatment methods

Symptom	Main group I (n=16)		Main group II (n=16)		Control group (n=12)	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Pruritus	3,0±0,0 (3)	0,06±0,06 (0)	2,94±0,06 (3)	0,75±0,14 (1)	3,0±0,0 (3)	2,0±0,12 (2)
Rash	3,0±0,0 (3)	0 (0)	2,94±0,06 (3)	0,31±0,12 (0)	2,83±0,11 (3)	1,33±0,14 (1)

Note. The dynamics of indexes is statistically significant at  $p < 0.001$  with Student's t and Wilcoxon tests in all groups.

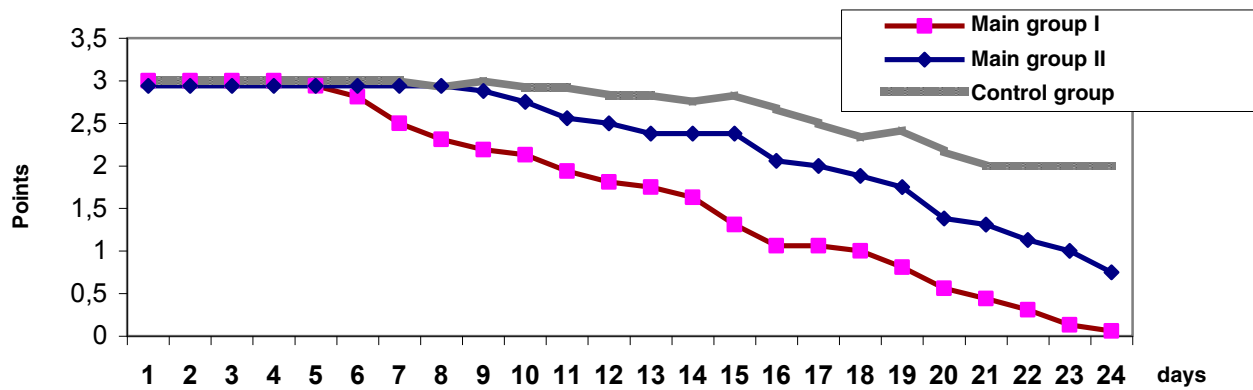


Fig. 2. Dynamics of average value (M) of severity of pruritus in patients with chronic urticaria for different treatment regimens

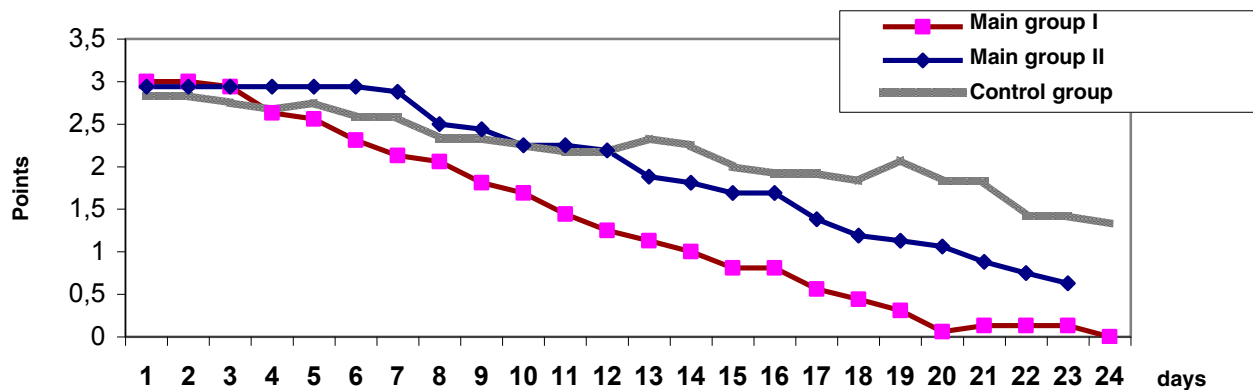


Fig. 3. Dynamics of the average value (M) the severity of rash in patients with chronic urticaria for different treatment regimens

In patients of the control group who have received only a combination of antihistamines and antileukotriene agents the clinical manifestations of the disease after completion of treatment have not entirely disappeared, but their intensity is decreased (see. Table. 3).

Comparative analysis of the severity of clinical symptoms in all groups showed its close correlation with the method of treatment: the correlation coefficients for the intensity of pruritus were  $r = 0,86$  ( $P < 0.001$ ), for a rash -  $r = 0,78$  ( $P < 0.001$ ). At the same time, significant differences (from  $p < 0.05$  to  $p < 0.001$ ) of the clinical effect of therapy with Bionorm and probiotic agent that containing *Lactobacillus reuteri* Protectis, have been observed from 5th (rash) and 7th (pruritus) day of therapy (see. Fig. 2 and 3).

### Conclusions:

1. In order to achieve a clinical effect in patients with chronic urticaria the therapeutic complex which affects to all parts of pathogenesis of the disease in this patient should be prescribed.

2. Inclusion in the complex of treatment regimens of patients with chronic urticaria Bionorm agent and probiotics which are containing *L. reuteri* Protectis BioGaia allows more significantly to reduce the histamine levels in the blood plasma in comparison with the appointment of only antihistamine and antileukotriene agents, as confirmed by the identified correlation ( $r = 0,68$ ) between the indexes and methods of treatment.

3. Inclusion of Bionorm agent into a treatment complex can significantly improve the qualitative and quantitative

composition of microflora, leading to a decrease of clinical symptoms, because the histaminase production process inactivating histamine is reverted.

4. In case of treatment with Bionorm agent a significant decrease in the intensity of pruritus and rashes is marked to the end of the first week of therapy with the complete reduction of clinical symptoms after the finishing the course of treatment.

5. Urticaria has different forms and variants of the clinical course, so it is necessary to use the appropriate approaches to the diagnosis and treatment of this disease.

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## СУЧАСНІ ПІДХОДИ ДО ПАТОГЕНЕТИЧНОГО ЛІКУВАННЯ ХРОНІЧНОЇ КРОПИВ'ЯНКИ

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### Резюме

В ході дослідження під нашим спостереженням знаходилися 44 хворих на хронічну кропив'янку віком від 18 до 65 років (середній вік  $46,1 \pm 2,0$  років), із них 13 (29,5 %) чоловіків і 31 (70,5 %) жінка.

Дослідження проводилося в дизайні паралельних груп. Всі пацієнти були рандомізовані на три клінічні групи залежно від схеми лікування.

Порівняльний аналіз впливу різних схем лікування на динаміку рівня гістаміну в сироватці крові хворих на хронічну кропив'янку показав високий ступінь кореляції ( $r = 0,68$ ;  $p < 0,001$ ) темпів зниження продукції гістаміну після лікування з комплексом лікувальних заходів (включення в терапію препарату Біонорм). Аналіз ефективності терапії дисбіозу кишечника у хворих на хронічну кропив'янку показав істотне поліпшення стану мікрофлори кишечника в основних групах пацієнтів ( $p < 0,01$ ). Нормалізація якісного і кількісного складу мікрофлори спостерігалася у 13 (81,3 %) пацієнтів, які отримували Біонорм, і у 11 (68,8 %) пацієнтів, які отримували пробіотик.

Результати дослідження показали, що нормалізація продукції гістаміну в плазмі крові та відновлення мікрофлори кишечника у хворих на хронічну кропив'янку при включенні в терапевтичний комплекс препарату Біонорм і пробіотика зумовлює істотне поліпшення основних клінічних симптомів захворювання.

Доведено, що існує кореляційний зв'язок між зниженням рівня гістаміну в плазмі крові та методом лікування.

Включення у терапію препарату Біонорм дозволяє досягти зниження рівня гістаміну та відновити флору кишечника, а отже, значно покращити клінічний ефект та якість життя пацієнтів.

**Ключові слова:** висип, свербіж, кропив'янка, гістамін, дисбіоз, кишечник.

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## THE MODERN APPROACHES TO PATHOGENETIC TREATMENT OF PATIENTS WITH CHRONIC URTICARIA

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### Summary

The effectiveness of different treatment methods in patients with the chronic urticaria has been studied.

The paper shows the serum histamine dynamics in patients with chronic urticaria that is influenced by different treatment complexes and (all patients were randomized in three groups).

There had been proven that a correlation exists between serum histamine decrease and treatment method.

Introducing Bionorm agent into the treatment allows to obtain the histamine level decrease, and correspondingly to improve significantly clinical effect and patients life quality.

**Key words:** rash, pruritus, urticaria, histamine, disbiosis, intestinal tract.

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