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МИКРОБИОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА БИОЦЕНОЗА КИШЕЧНИКА АМБУЛАТОРНЫХ ПАЦИЕНТОВ, ИМЕЮЩИХ ПОВЕДЕНЧЕСКИЕ ФАКТОРЫ РИСКА ХРОНИЧЕСКИХ НЕИНФЕКЦИОННЫХ ЗАБОЛЕВАНИЙ

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Microbiological Characteristics of Intestinal Biocenosis of Ambulator Patients Having Behavioral Risk Factors for Chronic Non-Communicable Diseases

Резюме

Наиболее ранняя коррекция поведенческих факторов риска хронических неинфекционных заболеваний позволит снизить показатели преждевременной смертности населения. В настоящее время недостаточно изучена взаимосвязь измененного спектра микрофлоры кишечника при различных показателях субоптимального статуса здоровья и индекса массы тела. Находясь в состоянии субоптимального статуса здоровья, пациенты считают себя здоровыми и длительно не обращаются к врачу, что затрудняет реализацию ранних профилактических мероприятий у данной группы пациентов. **Цель.** Определить качественный и количественный состав микрофлоры кишечника до и через 1 месяц после приема метапребиотического комплекса, содержащего пищевые волокна (инулин) и олигосахариды (олигофруктозу), у амбулаторных пациентов, имеющих поведенческие факторы риска хронических неинфекционных заболеваний. **Материалы и методы.** Проведено обследование амбулаторных пациентов (114 чел.: 36 мужчин, 78 женщин в возрасте от 18 до 72 лет). Проведено обследование, включающее расспрос с детализированным активным сбором жалоб (в том числе с помощью международного опросника SHSQ-25) и анамнеза и тщательный физикальный осмотр с антропометрическим исследованием. Методом MALDI-ToF масс-спектрометрии определены степень микробиотических нарушений, структура микрофлоры кишечника с идентификацией выделенных из фекалий микроорганизмов до приема и после приема курса метапребиотического комплекса при различных показателях субоптимального статуса и индекса массы тела. **Результаты.** Получены новые данные о биоценозе кишечника пациентов, считающих себя здоровыми, при различных уровнях субоптимального статуса. При применении метапребиотического комплекса, содержащего инулин и олигофруктозу, обнаружено улучшение состава микрофлоры кишечника за счет снижения частоты выделения грамотрицательных микроорганизмов (медиана степени

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обсемененности: от 0,45 (0,3-0,98) до 0,3 (0,21-0,7) при низких показателях субоптимального статуса и от 0,5(0,7-1,7) до 0,31(0,2-1,3) при высоких), и повышения частоты выделения энтерококков (медиана степени обсемененности: от 5,58 (4,16-7,0) до 6,3 (4,8-7,8) при низких показателях субоптимального статуса и от 4,5 (2,8-6,3) до 5,1 (3,8-6,4) при высоких). **Заключение.** Доказана значимость изучения микробиотического комплекса кишечника при повышении показателей субоптимального статуса здоровья и индекса массы тела у пациентов, считающих себя здоровыми, что позволит проводить наиболее раннее выявление и рациональную индивидуальную профилактику хронических неинфекционных заболеваний.

Ключевые слова: *метапребиотики, факторы риска заболеваний, микробиоценоз кишечника*

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Abstract

The earliest correction of behavioral risk factors for chronic non-communicable diseases will reduce the rates of premature mortality of the population. Currently, the relationship between the altered spectrum of intestinal microflora in various indicators of suboptimal health status and body mass index is not sufficiently studied. When they are in a state of suboptimal health status, patients consider themselves healthy and do not go to the doctor for a long time, which makes it difficult to implement early preventive measures in this group of patients. Goal. To determine the qualitative and quantitative composition of the intestinal microflora before and 1 month after taking a metaprebiotic complex containing dietary fiber (inulin) and oligosaccharides (oligofructose) in outpatient patients who consider themselves healthy, have behavioral risk factors for chronic non-communicable diseases or chronic non-communicable diseases in remission, and/or do not consult a doctor within the last 3 months. **Materials and methods.** Outpatient patients were examined (114 people: 36 men, 78 women aged 18 to 72 years). A survey was conducted, including a detailed active collection of complaints (including using the international SHSQ-25 questionnaire) and anamnesis, as well as a thorough physical examination with an anthropometric study. Using the MALDI-ToF mass spectrometry method, the degree of microbiotic disorders, the structure of the intestinal microflora was determined with the identification of microorganisms isolated from feces before and after taking the course of the metaprebiotic complex with various indicators of suboptimal status and body mass index. **Results.** New data were obtained on the intestinal biocenosis of patients who consider themselves healthy at different levels of suboptimal status. When using a metaprebiotic complex containing inulin and oligofructose, an improvement in the composition of the intestinal microflora was found due to a decrease in the frequency of release of conditionally pathogenic enterobacteria and other gram-negative microorganisms (median degree of contamination: from 0.45 (0.3-0.98) to 0.3(0.21-0.7) at low suboptimal status and from 0.5(0.7-1.7) to 0.31 (0.2-1.3) at high) and increase the frequency of enterococcal excretion (median degree of contamination: from 5,58 (4,16-7,0) to 6,3 (4,8-7,8) at low suboptimal status and from от 4,5 (2,8-6,3) to 5,1 (3,8-6,4) at high). **Conclusion.** The importance of studying the microbiotic complex of the intestine in increasing the indicators of suboptimal health status and body mass index in patients who consider themselves healthy is proved, which will allow for the earliest detection and rational individual prevention of chronic non-communicable diseases.

Key words: *metaprebiotics, disease risk factors, the intestinal microbiota*

Conflict of interests

The authors declare no conflict of interests

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CNCDs — chronic noncommunicable diseases, MPC — meta-prebiotic complex, RF — risk factors, SHS — suboptimal health status

Introduction

Socially significant chronic noncommunicable diseases (CNCDs) lead in the structure of morbidity, early disability and premature mortality in Russia and other developed countries [1]. Socially significant CNCDs include cardiovascular (hypertensive disease, myocardial infarction, stroke) and gastrointestinal diseases (gastric ulcer, pancreatitis, hepatitis, dysbiosis, dysfunction of small and large intestines), oncological, neuropsychiatric, respiratory and metabolic diseases (atherosclerosis, overweight, obesity) [1]. They are caused by the following risk factors (RF): unhealthy lifestyles, economic hardships and an adverse environment [2]. Many RF of CNCDs are interrelated and enhance each other, increasing the likelihood of these diseases [3]. The relationship between the altered spectrum of the species and the quantitative composition of gut microbiota with RF of CNCDs was proved [4–6]. Various representatives of normal microflora actively and steadily interact with a body, and changes in their composition are often secondary and reflect changes in the balance of microbiocenosis. Disorders of gut microbiota are manifested by an imbalance of the quantitative and qualitative composition of normal microflora that creates conditions for the excessive development of micromycetes, opportunistic and pathogenic flora [7]. These changes induce and support a «pro-inflammatory» environment, which is typical for pathological processes at the preclinical stage of diseases [3, 5]; they are manifested by the suboptimal health status (SHS) and cause functional dyspepsia and other diseases [8]. Patients with SHS consider themselves healthy and do not seek medical attention [9].

Early diagnosis and reversal of gut microbiota changes can be an additional tool to improve the quality of life of outpatients at the preclinical stage of disease. Probiotic agents (containing bifidobacteria and lactobacilli) were found not effective enough to correct microflora [10, 11]; not more than 0.0001% of probiotic microorganisms survive in the gastrointestinal tract of animals, and no more than 0.000000008% of lactobacilli survive in the human gastrointestinal tract [12]. The competition for the nutritious substrate between probiotic bacteria and their microbiota was proved, especially when prescribing drugs without considering the features of its species composition [13, 14]. Prescribing probiotics after treatment of patients with antibiotics does not always contribute to the restoration of their microbiota; sometimes, it even impedes it [15]; this may be due to the strain specificity of the species of microorganisms in the ecosystem of a particular patient. A more effective method for correcting gut microbiota disorders is the creation of a favorable environment for their habitation and good nutrition, using substances containing exometabolites (calcium lactate) and fruit polysaccharides (inulin and oligofructose) that are a growth medium.

This article presents the results of a dynamic study of the qualitative and quantitative composition of gut microbiota (culture) of outpatients who consider themselves healthy when using a meta-prebiotic complex (MPC) containing dietary fiber (inulin) and oligosaccharides (oligofructose) (STIM Lax, OOO V-MIN+, Russia).

Objective

To determine the qualitative and quantitative composition of gut microbiota one month before and after taking meta-prebiotic complex containing dietary fiber (inulin) and oligosaccharides (oligofructose), in outpatients with behavioral risk factors for chronic noncommunicable diseases.

Material and Methods

The study included the following outpatients: 114 individuals (36 male, 78 females aged 18 to 72 years). Inclusion criteria: patients who consider themselves healthy and/or who have not visited a physician during the last three months, who have behavioral RF of socially significant CNCDs or socially significant CNCDs in remission, who came to the clinic for any reason and/or were invited by the attending general practitioner for a routine examination. Exclusion criteria: clinically significant health disorders (acute diseases, acute CNCDs or decompensated conditions associated with CNCDs, infectious or oncological diseases) and/or visiting a physician during the last three months. In accordance with the Helsinki Declaration (1975, 1983, 1989), the participants were acquainted with the objectives and general provisions of the study and signed voluntary informed consent for this study. The Bioethics Committee of the Samara State Medical University (protocol No. 200 of May 22, 2019) approved the study protocol.

A routine clinical examination was performed, which included detailed questioning with active gathering of complaints (also using the SHSQ-25 international questionnaire) [9] and medical history, and thorough physical examination with anthropometric measures (measurement of height, body weight, waist circumference and hip circumference). BMI and waist/hip ratio were calculated for all patients depending on gender, age and suboptimal health status. Other RF of CNCDs were not taken into consideration in this part of the study. In order to identify and evaluate the relationship between RF of CNCDs and present functional diseases of the gastrointestinal tract that are not currently considered in the prevention of CNCDs, the species composition of the gut microbiota was defined with the identification of microorganisms isolated from feces using MALDI-ToF mass spectrometry. Two to three grams of feces were delivered to the laboratory in a sterile vial with no preservative within two hours of sampling. Culturing was carried out using an extended list of artificial nutrient media under aerobic and anaerobic conditions. Primary isolation of the material was carried out on 5% blood agar, bismuth-sulfite agar, SS agar, selective medium for the isolation of obligate anaerobic microorganisms, universal chromogenic medium, mannitol agar, medium for selective isolation of clostridia, lactobacilli, bifidobacteria, Saburo medium (HiMedia, India). Anaerobic conditions were created using gas generating pouches (Anaerogaz, Russia). Cultures were identified using a Microflex LT device (Bruker Daltonik GmbH, Germany). The study group included «conditionally healthy» patients with suboptimal health status. The comparison group included «conditionally healthy» patients with no suboptimal health status. The extent of microbiotic disorders was determined [«Protocol of Patient Management. Intestinal Dysbiosis» OST 91500.11.0004-2003]; relative values (presence or absence) were compared for particular groups of microorganisms for 1 g of intestinal contents, as well as microbial diversity in patients with low and high suboptimal health status depending on the duration of MPC intake. The specified parameters were determined before taking MPC and in 78 individuals one month after the course (with a dose of three tablets per day for two months) of MPC. Depending on the duration of intake of the meta-prebiotic STIM Lax complex, patients were divided into three groups: group 1, 61 subjects with full course of MPC (two months), group 2, 32 subjects with an incomplete course (from 1 to 2 months), and group 3, 21 subjects with a course of less than one month. The duration of IPC intake was in accordance with the desire of the patients. Partial or complete refusal to take MPC was associated with the following reasons: feeling of well-being (patients considered themselves healthy); active social life and unwillingness to visit outpatient clinics, change lifestyle and take drugs; economic reasons. The parameters of suboptimal health status were calculated (SHS: total score of SHSQ-25 equal to 13 or more indicated a suboptimal health status that requires further examination of the patient) [9] and body mass index (BMI according to the formula: body weight, in kg/height, in m^2; obesity grade was assessed according to WHO criteria, 1997); quantitative parameters of gut microbiota diversity and its microbial load. Statistical analysis was carried out using Microsoft Office Excel 2010 and Statistica 13.3 software package (Statsoft, USA) with an assessment of the normality of distribution. The required number of observations was calculated by the following formula: $N = t^2 x\ \sigma^2 / \Delta^2$, where N is the number of observations, t is the confidence coefficient depending on the given level of probability (p = 95%) of the final result, σ is the standard deviation, and Δ is the margin of error. The normality of distribution was checked using the Shapiro–Wilk test; differences between groups were evaluated using nonparametric analysis (Mann–Whitney, Kruskal–Wallis tests) at a significance level of $p < 0.05$. This clinical study was consistent with the principles of the Law on the Circulation of Medicines No. 61, of April 12, 2010, and the principles of Good Clinical Practice.

Results

Table 1 presents general characteristics of patients. In accordance with the goals and objectives of the study, BMI and waist/hip ratio were calculated for the entire cohort of patients depending on their gender and age. Other RF of CNCDs were not taken into consideration in this part of the study. A high BMI was more often observed in women than in men (39 individuals, 34.1% and 14 individuals, 12.3%, respectively), along with high suboptimal health status (women with high SHS — 33 individuals, 28.9%; women with low SHS — 19 individuals, 16.7%). There were no significant differences in the groups according to the waist/hip ratio. It is known that the better the person's well-being, the lower the value of suboptimal health status determined by the SHSQ-25 scale. A significant proportion of patients (65 patients, 57.0%) who considered themselves healthy had high suboptimal health status values and were part of the observation group. Patients with high suboptimal health status values were older and had high BMI ($p < 0.05$).

Parameters of the microbial load in the studied groups of patients are presented in Table 2. An initial examination of the patients revealed a reduced quantitative composition of the populations of microorganisms. When comparing the microbial composition before and after taking MPC, depending on the suboptimal status, significant differences were found in the groups of gram-negative flora, represented by nonenzymatic gram-negative bacteria and enterococci.

Data on differences in microbial diversity in groups of patients depending on the duration of MPC intake (Table 3) were obtained; the data did not depend on parameters of suboptimal health status. As early as the diagnosis stage, patients could be divided into three groups comparable in clinical characteristics: patients fully complying with the physician's recommendations;

Table 1. General characteristics of patients

Sign	SHS n=114*		Reliability**	Overweight n=114*		Reliability**
	Comparison group, SHS <13 Mean + Std n=49 (Me(IQR))	Observation group, SHS ≥13 Mean + Std n=65 (Me(IQR))		<24,9 n=61	≥25,0 n=53	
Age (Me(IQR)) n=114	42,0 (25,3-47,4) n=49	46,1 (34,4-62,7) n=65	**z=4,15; p=0,003**	47,0 (31-57) n=61	43,5 (35-57) n=53	**z=3,3; p=0,007**
Male age (Me(IQR)) n=62	42,5 (32,0-58,0) n=30	48,0 (29,0-52,1) n=32	**z=3,8; p=0,028**	41,0 (31,0-47,0) n=48	45,6 (33,0-48,0) n=14	**z=0,71; p>0,05**
Women age (Me(IQR)) n=52	35,1 (23,0-49,0) n=19	44,0 (38,5-56,5) n=33	**z=4,003; p=0,0004**	38,5 (30,0-48,0) n=13	43,2 (24,0-51,0) n=39	**z=4,74; p=0,045**
Waist-hip ratio in men (Me(IQR)) n=62	0,85 (0,83-0,92) n=30	0,94 (0,91-0,96) n=32	**u=6,0; z=0,0; p=1,0**	0,83 (0,80-0,87) n=48	0,93 (0,90-0,95) n=14	**u=0,0; z=0,0; p=1,0**
Waist-hip ratio in women (Me(IQR)) n=52	0,77 (0,75-0,89) n=19	0,82 (0,79-0,91) n=33	**u=0,0; z=0,0; p=1,0**	0,75 (0,67-0,79) n=13	0,95 (0,88-0,99) n=39	**u=0,0; z=0,0; p=1,0**

Note:
*n — number of observations
** u — the Mann-Whitney test; z — the number of standard deviations from the average value of the data point; p- the level of statistical significance

Table 2. Microbial composition (median degree of contamination) before and after taking Mc, depending on the suboptimal status*

Признак/ Attribute		Всего/ Total n=114 (100%)*			
		Группа сравнения / Comparison group, SHS <13 n=49 (43,0%)		Группа наблюдения / Observation group, SHS ≥13 n=65 (57,0%)	
		До приема МПК/ Before taking Mc** Mean + Std (Me(IQR))	После приема МПК/ After taking Mc** Mean + Std (Me(IQR))	До приема МПК/ Before taking Mc** Mean + Std (Me(IQR))	После приема МПК/ After taking Mc** Mean + Std (Me(IQR))
Bifidobacteria	p>0,05***	3,1 (2,8-3,89)	3,4 (3,1-3,9)	3,0 (2,6-3,3)	3,23 (2,5-3,34)
Lactobacilli	p>0,05	5,3 (4,8-5,6)	5,8 (5,4-6,7)	5,5 (4,8-5,4)	5,6 (5,2-6,1)
Lactic acid streptococcus	p>0,05	0,1 (0,05-0,11)	0,12 (0,06-0,14)	0,08 (0,05-0,1)	0,06 (0,04-0,09)
Clostridium	p>0,05	0,09 (0,03-0,1)	0,2 (0,1-0,5)	0,4(0,2-0,45)	0,6(0,4-0,9)
Escherichia	p>0,05	4,1(3,3-4,3)	5,2(3,4-6,1)	4,6(4,1-5,2)	5,3(3,9-5,4)
Opportunistic flora	p>0,05	0,8 (0,56-1,7)	0,6 (0,4-1,2)	0,9 (0,6-1,84)	0,8 (0,5-1,4)
Gram-negative flora	**p<0,05**	**0,45 (0,3-0,98)**	**0,3 (0,21-0,7)**	**0,5(0,7-1,7)**	**0,31(0,2-1,3)**
Staphylococcus aureus	p>0,05	0,3(0,15-0,45)	0,0	0,54(0,3-0,9)	0,0
Other staphylococci	p>0,05	0,2(0,0-1,1)	0,3(0,0-0,05)	0,1(0,0-1,3)	0,2(0,1-0,9)
Enterococci	**p<0,05**	**5,58(4,16-7,0)**	**6,3(4,81-7,79)**	**4,5(2,75-6,25)**	**5,1(3,75-6,44)**
Yeast	p>0,05	0,4(0,0-0,81)	0,3(0,0-0,5)	0,7(0,0-1,4)	0,4(0,0-1,36)
Mold fungi	p>0,05	0,2(0,0-0,43)	0,0	0,31(0,0-0,81)	0,0

Note:
*n — number of observations
**Mc — Metaprebiotics complex
***p — the level of statistical significance

Table 3. Microbial diversity of intestinal biocenosis depending on the duration of Mc intake*

Indicator	Before taking Mc* n=114**			After taking Mc* n=114**			Reliability***		
	Group 1. n=26	Group 2 n=28	Group 3 n=60	Group 1. n=26	Group 2 n=28	Group 3 n=60	Group 1. n=26	Group 2 n=28	Group 3 n=60
Microbial diversity Mean + Std (Me(IQR))	7,8 (7,2-8,8)	9,1 (8,5-9,4)	9,2 (7,3-9,6)	8,1 (7,2-9,1)	9,45 (8,5-9,73)	9,78 (8,62-11,3)	**z=0,1; p=0,93**	**z=4,73; p=0,042**	**z=4,12; p=0,003**

Note:
*Mc — Metaprebiotics complex
**n — number of observations
*** z — the number of standard deviations from the average value of the data point; p — the level of statistical significance

*Table 4. Differences in suboptimal status indicators before and after the course intake of Mc**

Подгруппа/ Subgroup	SHS до курса МПК/ SHS before the Mc course Mean + Std (Me(IQR))	SHS после курса МПК/ SHS after the Mc course Mean + Std (Me(IQR))	Достоверность/ Reliability***
All patients n=114	19,3 (10,8-25,6)	11,2 (7,4-16,9)	p <0,0001
Women n=78	19,1 (11,4-25,8)	11,8 (8,3-17,1)	p <0,0001
Men n=36	13,5 (5,9-19,7)	9,2 (7,7-14,2)	p=0,0004
Patients under 30 years of age n=22	14,8 (9,6-17,3)	11,2 (8,7-14,6)	p=0,0052
Patients over 30 years of age n=91	19,5 (14,3-22,4)	11,6 (10,9-19,8)	p <0,0001
Receiving Mc less than 1 month n=22	14,9 (12,5-16,8)	14,6 (12,1-16,4)	p=0,23**
Receiving MC from 1 month to 2 months n=30	18,6 (12,7-23,4)	12,1 (8,2-15,9)	p <0,0001
Admission of Mc full course (2 months) n=61	17,9 (11,8-26,1)	9,7 (6,7-13,9)	p <0,0001

*Mc — Metaprebiotics complex
** no significant difference
*** p — the level of statistical significance

patients partially following the recommendations, and patients not following the recommendations for various reasons. For patients who took the full course of MPC, improved microbiological parameters lasted even after the completion of the course.

Differences in the parameters of suboptimal health status before and after the course of MPC are presented in Table 4. Significant differences in all groups of patients were revealed: the general parameter of suboptimal health status decreased in all age groups, which indicates an improvement in the health parameters of the subjects. At the same time, the best values were obtained with the full course of MPC in two months.

Discussion

Mortality from CNCDs can be at least halved via the early diagnosis, identification and correction of individually significant behavioral RF [1–3] on an outpatient basis. A significant group (57%) of patients who were invited by the physician who considered themselves healthy and/or did not visit the physician had RF of CNCDs and had suboptimal health status. It was proven that increased body weight is one of the most important RFs of CNCDs that increase the probability of metabolic syndrome [2, 3]. Numerous studies proved the impact of changes in the quantitative and qualitative composition of gut microbiota on the utilization of nutrients and protection against aggressive environmental effects by increasing or reducing the risks of metabolic syndrome and comorbid pathology [4–6]. Many (45.6%) patients in our study had a high BMI with altered quantitative and qualitative parameters of gut microbiota. The studies showed that the composition of the gut microbiota can play a critical role in the development of obesity [4-6], and the microbiological phenomenon of dysbiosis is the initial stage of many concomitant diseases, which aggravates the course of the main pathological process [15]. There are contradictory reports about the relationship between group differences in the structure of the gut microbiota (for example, the presence of Bacteroidetes and Firmicutes) and the BMI of the host. However, taxonomic profiles have different patterns for obese and thin patients [4–6]. Our study found differences in the microbiotic status of outpatients depending on their body weight and the presence of suboptimal health status, as well as differences between normal gut microbiota and the accepted standards. The total number of microorganisms in excess of 10^7 (R. V. Epstein-Litvak, F. L. Vilshanskaya, 1970) or more than 10^8 (V. M. Bondarenko et al., 1995) is considered the reference range for intestinal flora. Most of our patients (57%) with suboptimal health status, according to these criteria, were characterized by insufficient total microflora (less than 10^7). MPC helped obtain positive results of the correction of intestinal biocenosis and improve the parameters of suboptimal health status.

Conclusion

The results revealed qualitative and quantitative changes in the gut microbiota of outpatients who consider themselves healthy and/or have not visited a physician in the last three months. The hypothesis about the possible role of the gut microbiota in the regulation of human gene expression (including genes associated with lipid metabolism, obesity and inflammation) enabled to conduct studies that revealed the participation of microbiota in the pathogenesis and sanogenesis of major noncommunicable human diseases [16]. The above data proved the relationship between differences in the microbiota composition of outpatients and their body weight and the presence of suboptimal health status. This determines the need for the earliest possible individual evaluation of gut microbiota during active screening for RF of CNCDs and the need to determine the criteria of microbiota changes in patients with socially significant CNCDs. The importance of developing up-to-date guidelines for gut microbiota evaluation is discussed in literature [16]. The representativeness of the sample of participants suggests that such standards are especially relevant for the category of patients with suboptimal health status. Our study proved the importance of the full course of MPC for the long-term maintenance of a high population level of normal microflora in cases of microbiome disorders as part of the complex correction of behavioral risk factors associated with suboptimal health status, which will prevent obesity and associated diseases in this category of patients.

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