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CONTENT

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ASSESSMENT OF THE INFLUENCE OF FACTORS ON THE TICK-BORNE ENCEPHALITIS AND SIBERIAN TICK-BORNE TYPHUS INCIDENCE IN AREAS WITH MIXED FOCI OF THESE INFECTIONS

Altai State Medical University, Barnaul

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The article presents the results of epidemiological research of combined foci of tick-borne viral encephalitis and Siberian tick-borne typhus, namely the results of the multidimensional factor analysis, through which the leading factors influencing epidemic processes of these infections were identified. The degree of influence of each of the factors on the level of current infections incidence was determined. A comparative assessment of the degree of influence of the leading factors on the incidence of the population of Altai Krai districts with combined foci of these infections was given.

Key words: *combined foci, natural focal infections, tick-borne viral encephalitis, Siberian tick-borne typhus, endemic territories, determination of leading factors, multidimensional factor analysis.*

Tick-borne infections are one of the urgent problems of modern epidemiology of natural focal diseases and their epidemic processes may be influenced by certain factors, determining aspects such as the activity of natural and anthropurgic foci and the frequency of contact of the population with these foci, which in turn influences the incidence rate trend. The impact of these factors measured separately can be regarded as statistically insignificant, while a combination of a large number of similar factors may have a significant impact on the epidemic process of current natural focal infections.

Assessment of the hidden relationship between a set of individual predictors, allowing to form groups of leading factors with determination of the degree of their influence on the resulting sign (Siberian tick-borne typhus and tick-borne viral encephalitis incidence) can provide an opportunity to re-evaluate the contribution of each predictor to the epidemic processes of the studied infections. The use of multidimensional factor analysis is one of the methods of modeling the structure of leading factors influencing epidemic processes of tick-borne viral encephalitis (TVE) and Siberian tick-borne typhus (STT) in the Altai Krai areas with combined foci of these infections. Having such data will allow to correctly optimize a set of preventive measures aimed at reducing the incidence rate of current natural focal infections among the population.

The aim of the study was to determine the groups of leading factors influencing the epidemic processes of tick-borne viral encephalitis and Siberian tick-borne typhus in the Altai Krai territory of combined foci, as well as to assess the extent of their impact on the incidence of these infections.

Materials and methods

The study was conducted using the data of the official reporting of the Federal Service for Consumer Rights and Human Welfare Protection, the Center of Hygiene and Epidemiology in Altai Krai, the Ministry of Health of Altai Krai, the Federal Statistics Service for Altai Krai, the data of statistical reporting forms No. 2 "Information on infectious diseases" in Altai Krai for 2000–2018. The study used the calculation of absolute and relative values, mean values (X), coverage errors (±m), the calculation of significance of differences was carried out using the Fisher test (f). Processing of the obtained statistical data was conducted in Statistica 12.0. Reduction of data dimension in calculations was carried out by the method of main components. Rotation of factor loads was carried out by the Varimax method. The determination of the leading predictors influencing the TVE and STT incidence was carried out on the basis of the proper calculated values of these predictors taking into account the Kaiser criterion.

Results and discussion

A set of predictors selected empirically and subject to annual statistical accounting has been determined for multidimensional factor analysis (statistical collections of the Federal Service on Surveillance in the Sphere of Consumer Rights Protection and Human Welfare, materials of the Ministry of Health of the Russian Federation, Federal State Statistics Service). The indicators related to the Altai Krai areas with combined foci of TVE and STT which were also characterized by a high level of incidence compared to Altai Krai as a whole were taken into account.

Three groups of predictors were formed for the factor analysis:

Group 1 was formed of predictors providing the frequency of contacts of population of areas with causative agents of STT and TVE in the areas with combined foci of these infections (the number of the working-age population, the number of

children and adolescents up to the age of 17, the number of occupational risk cohort among the population, the number of population older than the working age, the prevalence of ticks with rickettsia, infected ticks, the number of ticks per 1 km of the way). This group of predictors ensures the formation of a tendency to increase in the STT and TVE incidence rate;

Group 2 was formed of predictors ensuring the implementation of primary and secondary prevention of current nosologies, as well as the availability of medical care to persons affected by tick bite (the number of medical organizations, including FAS and outpatient clinics, the number of beds in in-patient hospitals, the area of acaricide treatment, rates of vaccination against TVE and immunoprophylaxis using immunoglobulin against TVE). This group of predictors ensures the formation of a downward trend in the STT and TVE incidence rate in the Altai Krai areas with combined foci;

Group 3 was formed of predictors providing the formation of natural and anthropurgic foci of STT and TVE, as well as maintaining their high activity (livestock in farm and personal subsidiary holdings, the area of perennial plantings near roads, the length of auto-roads put into service, the area of seed cultures). This group of predictors provides the formation of a tendency to increase in current infections incidence rates.

Within the framework of the multidimensional factor analysis, we conducted an assessment of the influence of three groups of formed predictors on the TVE and STT incidence among the population of areas with combined foci of STT and TVE in order to determine the leading predictors and exclude "noise" ones, which do not have significant influence.

After determining the leading predictors within each of the three formed groups, their ranking was carried out according to the criterion of the share of total variance (%), expressing the degree of influence of the analyzed predictors on the TVE and STT incidence among the population of areas with combined foci of current infections. When ranking, all predictors (previously defined as the leading ones) were subjected to multidimensional factor analysis, which where then combined into factors using the method of main components, on the basis of calculated values of factor loads. At the same time, it was possible to establish that most predictors have no connection with other analyzed predictors and form factors independently. For example, **Factor 1** was formed of predictors characterized by the population in the group of high risk of disease of these nosologies (the number of children and adolescents up to the age of 17, the number of occupational risk cohort among the population, the number of population older than the working age), as well as reflecting the availability of curative and preventive care for the population (the number of medical organizations, including FAS and outpatient clinics). The other factors were formed by one of the predictors independent of the others: **Factor 2** – the number of ticks per 1 kilometer of the way; **Factor 3** – the area of acaricide treatment; **Factor 4** – the index of infected ticks (%); **Factor 5** – the prevalence of ticks with rickettsia (%); **Factor 6** – the indicator of preventive vaccination against TVE; **Factor 7** – the indicator of immunoglobulin seroprevention for TVE.

A multidimensional factor analysis allowed to determine the extent to which each of the factors affect the incidence of current infections. The presence of non-specific factors influencing trends in the incidence of TVE and STT infections different in nosology was also found. Thus, the group of non-specific factors (factors 1–3) is characterized by the degree of influence on the dynamics of incidence in population: TVE – 80.46%, STT – 85.31%. At the same time, each of the nosologies has a set of specific factors that selectively influence the tendency of the STT or TVE incidence. Thus, a group of specific factors has a combined impact of 18.09% on the dynamics of the TVE incidence; STT – 11.61%. The share of "noise" factors influencing the trend of the STT incidence was 30.8%, and TVE – 1.45%. The data are presented in Table 1.

Conclusion

Thus, in the course of the conducted study, it was possible to establish that the TVE and STT incidence is more than 80% formed due to the influence of non-specific factors formed by such predictors as: in **Factor 1**, the population in the group of high risk of incidence of these infections (the number of children and adolescents up to the age of 17, the number of occupational risk cohort among the population, the number of population older than the working age), as well as the availability of curative and preventive care for the population (the number of medical organizations, including FAS and outpatient clinics); **Factor 2** – the number of ticks per 1 kilometre of the way; **Factor 3** – the area of acaricide treatment. At the same time, the predictors from **Factor 1** have a significant share of total variance equal to 64.49% for TVE and 64.91% for STT.

Predictors considered as preventive measures aimed at reducing the TVE and STT incidence have a degree of influence of 13.13% on the TVE incidence (the area of acaricide treatment – 4.52%, the indicator of preventive vaccination against TVE – 2.63%, the indicator of immunoglobulin seroprevention for TVE – 5.98%) and 4.71% (the area of acaricide treatment) – on the STT incidence. The low impact of preventive measures both in general and in isolation may be due to the insufficient volume of activities carried out. Awareness of the degree of influence of each predictor considered as measures of prevention of current natural focal in-

fections will allow to optimize the use of economic resources to reduce the incidence rate among the Altai Krai population living in areas with mixed foci of these infections.

Conflict of interest. The authors declare no conflict of interest.

Table 1

The results of the multidimensional factor analysis, expressed in the comparative assessment of the degree of influence of the leading factors on the TVE and STT incidence in Altai Krai areas with combined foci of these infections

List of factors formed of analyzed predictors	The degree of influence of the factor, %	
	Tick-borne viral encephalitis	Siberian tick-borne typhus
Non-specific factors		
Factor 1	64.49	64.91
Factor 2	11.45	15.69
Factor 3	4.52	4.71
Specific factors		
Factor 4	9.48	-
Factor 5	-	11.61
Factor 6	2.63	-
Factor 7	5.98	-

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EPIDEMIOLOGICAL FORECASTING OF THE INCIDENCE OF TICK-BORNE NATURAL FOCAL INFECTIONS IN WESTERN SIBERIA

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The developed technology of epidemiological forecasting of the incidence of tick-borne natural focal infections on the basis of neural network and GIS-technologies allows to obtain reliable prognostic incidence rates in endemic territories. Implementation of the technology provides taking into account more than 25 factors of biotic and abiotic nature, having a significant influence on the process of formation and maintenance of high activity of infection foci. This article presents epidemiological forecasting of the incidence of tick-borne encephalitis on the model of Altai Krai and the Republic of Altai.

Key words: *epidemiological forecasting, natural focal infections, tick-borne viral encephalitis, epidemic process.*

The territory of Western Siberia makes the main contribution to the formation of morbidity of tick-borne natural focal infections in Russia [1, 2]. Regions of the Siberian Federal District, located within the borders of Western Siberia, are endemic for such infections as tick-borne viral encephalitis, ixodic tick-borne borreliosis, rickettsiosis, West Nile fever, Kemerovo fever, anaplasmosis, ehrlichiosis, etc. [3–5]. The high intensity of contact of the population with infection sites is determined by the significant share of the rural population in more than 50% of the demographic structure of the regions, the employment of a significant part of the population in agriculture and forestry, as well as the presence of anthropurgic foci of infection within the boundaries of populated areas [6, 7].

At present, taking into account the natural migration of animal feeding mites through the territory of Western Siberia, which facilitates the transport of mites over long distances, the risk of spreading "new" pathogens of natural focal infections for regions of Siberia increases [8–10]. Thus, in the steppe regions of Altai Krai during the last decade, the occurrence of Ixodes and Haemaphysalis genus ticks previously not characteristic of these territories has been observed [11–13]. Detection of pathogens of several infections in ticks of these genera contributes to the formation of new foci of infections, increasing the risk of potential epidemic danger of infection of the population [14, 15].

The research objective is to develop a technology of epidemiological forecasting of the incidence of tick-borne natural focal infections in Western Siberia on the example of tick-borne viral encephalitis in model territories – Altai Krai and the Altai Republic.

Materials and methods

As the research materials, data of the Administration of the Federal Service for Consumer Rights and Human Welfare Protection in Altai Krai, the Administration of the Federal Service for Consumer Rights and Human Welfare Protection in the Altai Republic were used. The data of laboratory studies were obtained in collaboration with the Federal Budget Institution of Science "Central Research Institute for Epidemiology" of Rospotrebnadzor. Processing of data obtained in the course of the study was carried out using the Statistica 13.0 package programs, including neural networks, hierarchical cluster analysis. In the assessment of the spatial distribution of the studied phenomena across the territory of the Siberian Federal District regions, GIS technologies of the ArcGIS program were used.

Results and discussion

During the retrospective epidemiological analysis of the incidence of tick-borne encephalitis (TE) in the period from 2000 to 2017 in the Siberian Federal District (SFD), a pronounced downward trend was established: the population morbidity rate decreased from 15.4±0.17 $^0/_{0000}$ to 5.8±0.27 $^0/_{0000}$ respectively ($p<0.001$) with an average long-term rate of 10.1±0.23 $^0/_{0000}$. Also during this period, there was a decrease in the TE mortality rate from 0.14±0.03 $^0/_{0000}$ to 0.05±0.01 $^0/_{0000}$ ($p<0.001$). The method of autocorrelation determined the long-term cycle of TE incidence in the SFD, which amounted to 9 years and corresponded to the indicator of the long-term cycle of TE in the Russian Federation in general. This nosology was characterized by spring-autumn seasonal prevalence with the beginning of the registration of the first cases in April and the peak of morbidity in June (Figure 1).

In the structure of the average long-term TE incidence rate in the SFD in 2000–2017, the largest share of cases occurred in Krasnoyarsk Krai (33.6%), Tomsk Oblast (14.2%), Kemerovo Oblast (9.9%), Irkutsk Oblast (8.5%). Within the boundaries of the territory of these regions, there are multiple habitats of vector ticks, which determine the formation of natural and anthropurgic infection foci. A complex of natural climatic factors determining favorable habitat conditions for the existence of ticks and their feeders can also contribute to maintaining of the high activity of infection foci.

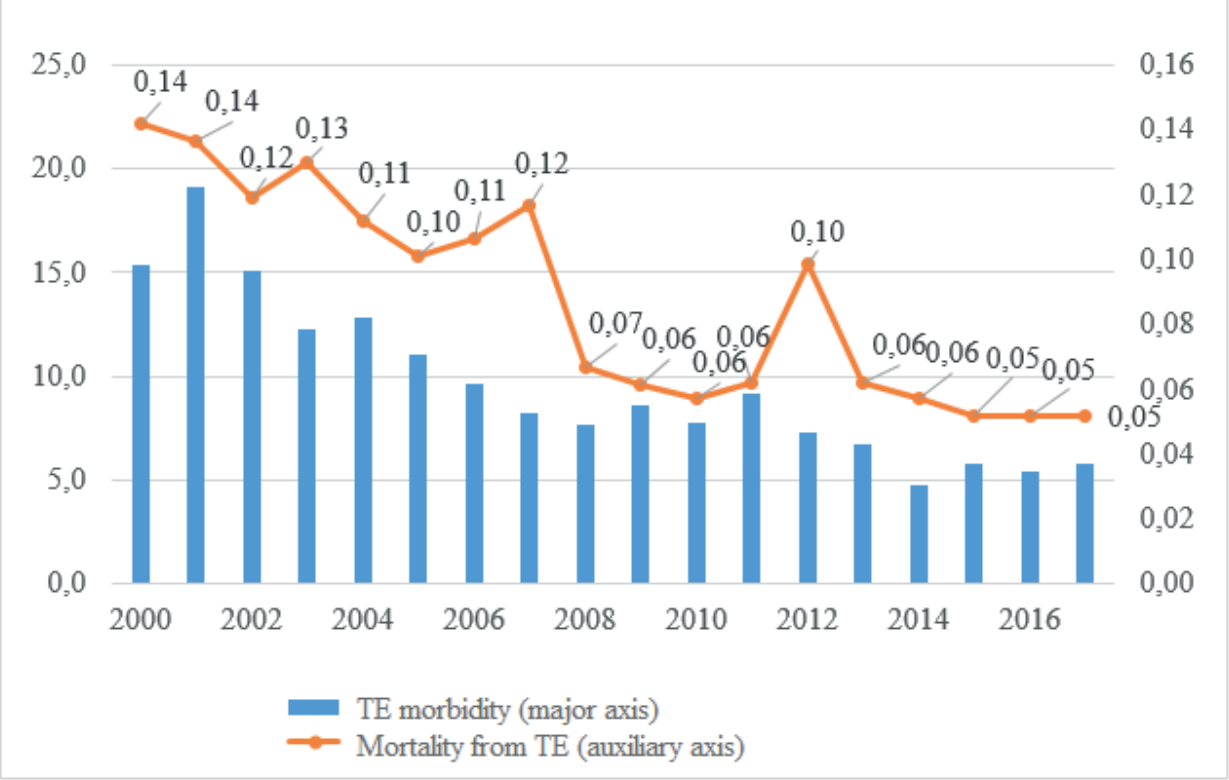

Figure 1. Dynamics of TE morbidity and mortality from TE in the SFD in 2000–2017 ($^0/_{0000}$).

One of the characteristics of the epidemic process of TE in the SFD in the period from 2000 to 2017 was the prevalence of morbidity of rural population over urban population by 27.5%. The average long-term morbidity rate of residents of rural areas of the SFD was 13.4±1.57 $^0/_{0000}$, urban – 9.7±0.84 $^0/_{0000}$. This situation was caused by the presence of regions with more than 50% of residents of rural areas in the demographic structure in the Siberian Federal District, including the Republic of Buryatia (80%), Zabaykalsky Krai (68%), the Altai Republic (68%), the Tyva Republic (67%), Omsk Oblast (66%), Altai Krai (50%), the Republic of Khakassia (40%).

The morbidity rate of TE among adults in the SFD was 8.7±0.82 $^0/_{0000}$, which is 39.7% higher than that of 6.2±1.39 $^0/_{0000}$ among children under 17. In the group of adult population, there were occupational risk groups, whose activity is mainly related to agriculture, forestry, tourism and tourism sectors of the economy in endemic regions. In 2000–2017, an average of 1321 cases of TE among the adult population were registered in the regions of the SFD annually, which is 6 times higher than the number of cases among children and adolescents aged up to 17. At the same time, 77.8% of all cases in the SFD among adults were provided by Irkutsk Oblast (96 cases annually), Novosibirsk Oblast (140 cases annually), Kemerovo Oblast (165 cases annually), Tomsk Oblast (185 cases annually), Krasnoyarsk Krai (442 cases annually).

In order to develop the technology of epidemiological forecasting of TE incidence in endemic regions of Western Siberia, model territories were determined within the boundaries of which there were active infection foci annually registered TE incidence among the population. Altai Krai and the Altai Republic were chosen as model regions, which was determined by consolidation of the leading factors within their borders contributing to the formation of the tendency to increase in the TE incidence. For the selection of model territories from the SFD regions, the analysis was carried out on the basis of hierarchical clustering, which was based on samples of factors of biotic and abiotic nature for the period from 1956 to 2017.

The Ward's method was chosen as the clustering method involving normalization of indicators of all samples with calculation of average values for each selected factor for analysis and unification of regions of the SFD into clusters. The obtained data allowed to allocate a model cluster, including Altai Krai and the Altai Republic, as well as a model-dependent cluster, including other SFD regions. On the basis of the obtained results, a dendrogram was designed reflecting the results of clustering (Figure 2).

Neural network models were developed for each of the model territories, which allowed to predict the incidence and number of victims of ticks sucking. Also, with the use of neural networks, promising volumes of preventive measures necessary for optimization of measures of TE incidence epidemiological control were determined.

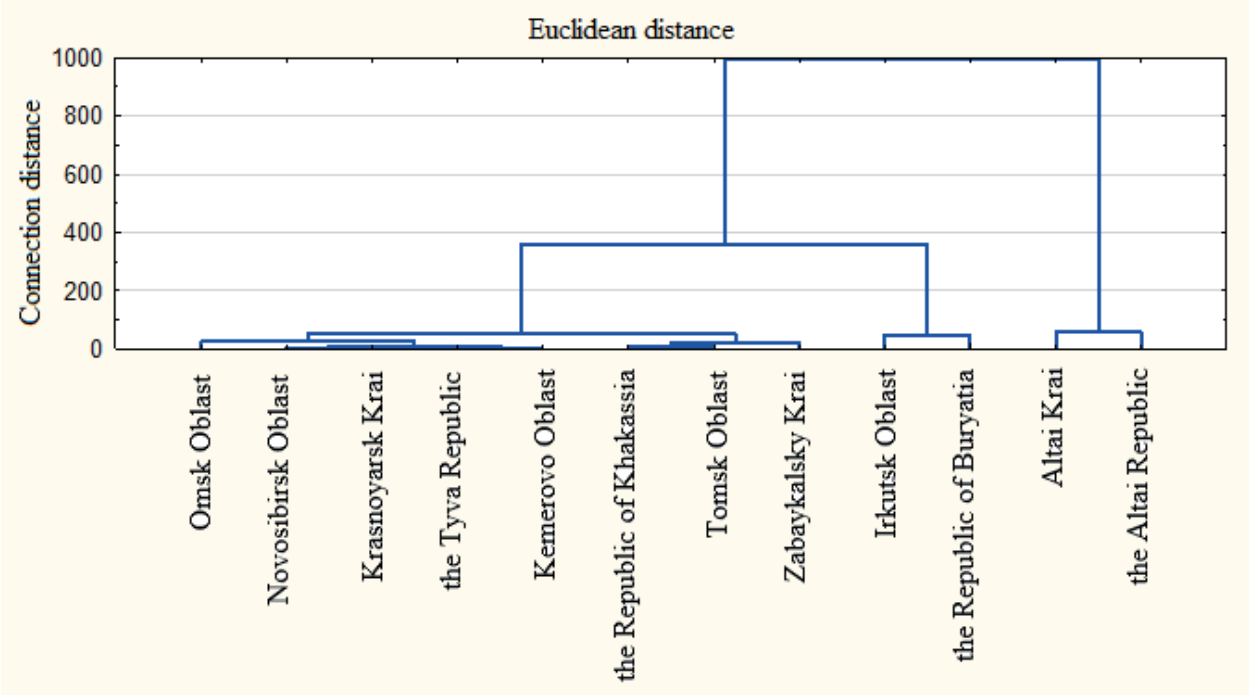

Figure 2. Dendrogram of hierarchical cluster analysis of SFD regions with the selection of model (1) and dependent (2) clusters.

The results of the study showed that for Altai Krai as a model territory, to reduce the TE incidence by 32.6% to 0.91 $^{0}/_{0000}$ in comparison with the indicator of the previous period, it is necessary to increase the volume of acaricide treatment by 10% to 2223.3 ha, increase the volume of seroprevention by 3.4% to 10000 doses per year, increase the volume of TE vaccination by 10% to 77500 doses per year. For the Altai Republic, in order to reduce incidence by 32.1% to 4.21 in comparison with the previous period, it is necessary to increase the area of acaricide treatment by 20% to 817.2 ha, increase the volume of seroprevention by 4.9% to 2300 doses per year, increase the volume of TE vaccination by 10% to 28500 doses per year.

In the framework of the conducted study, the natural migration processes of TE vector ticks on the territory of model regions were studied. It was

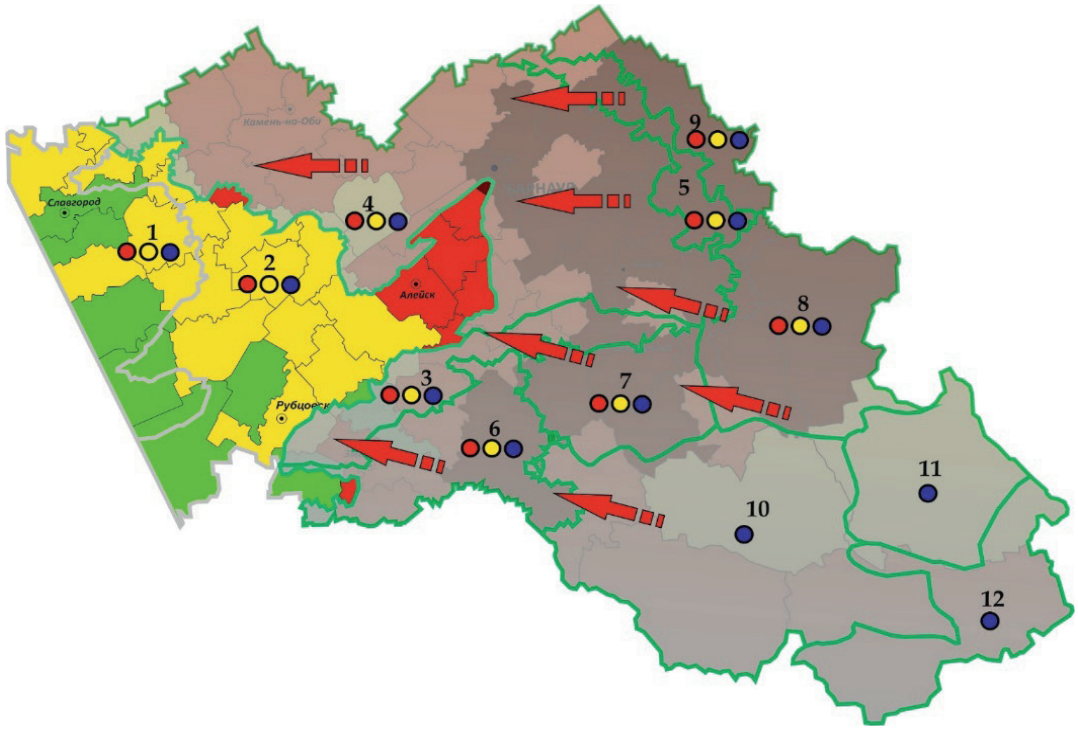

Figure 3. Map of the perspective spatial distribution of "new" pathogens of tick-borne infections on the territory of the model regions of Altai Krai and the Altai Republic.

found that the migration of ticks is directed from the south-eastern to the western borders of Altai, which causes the formation of new TE foci in the territories that were not previously endemic. The obtained data reflect the probability of an increase in the risk of infection of the SFD population in addition to TE by pathogens such as Kemerovo fever, R. tarasevich, Borellia myiamotoi, Anaplasma phagocytophillum, West Nile fever, etc. The results of the study of the perspective spatial distribution of "new" pathogens of tick-borne infections on the territory of the model regions of Altai Krai and the Altai Republic were mapped (Figure 3).

Conclusion

Epidemiological forecasting of the TE incidence in the SFD regions should be based on the analysis of a set of biotic and abiotic factors. In endemic territories of the SFD, manifestations of TE epidemic processes are characterized by identity and mutual dependencies, which is caused by the presence of common natural climatic complexes within the borders of Western Siberia. Changing conditions of the external environment under the influence of a complex of factors of biotic, abiotic and anthropogenic nature entail inevitable change of the epidemic situation and ensuring its operational monitoring.

Developed algorithms of neural network forecasting allow to provide calculation of the perspective indicators of TE incidence, number of victims of ticks sucking, and necessary amount of measures of epidemiological surveillance of morbidity. The results obtained with the consideration of neural network epidemiological forecasting allow to determine the perspective spatial distribution of "new" for model regions tick-borne infection pathogens and extrapolate the data to other TE endemic SFD regions.

Conflict of interest. The authors declare no conflict of interest.

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COMPARATIVE ANALYSIS OF SOME MANIFESTATIONS OF THE EPIDEMIC PROCESS OF CHICKENPOX IN BARNAUL AND ALTAI KRAI

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Chickenpox is a widespread highly contagious disease with an airborne transmission mechanism. The possibility of mass morbidity with this nosology determining the need for the introduction of quarantine measures preconditions the significance of the issue of primary specific prevention. A feature of chickenpox in children's groups is the outbreak of the infection among people who have no previous history of disease or have not been vaccinated. The study resulted in the establishment of several features of the epidemiological manifestations of chickenpox among children and adults in Altai Krai.

Key words: *chickenpox, epidemiology, vaccination, quarantine.*

Chickenpox is an acute viral infectious disease characterized by lesion of the skin and mucous membranes in the form of polymorphic maculo-papulo-vesicular rash, moderately pronounced fever and symptoms of general intoxication, mainly benign course [1]. Infection occurs in cases of absence of post-infective immunity or vaccination against chickenpox in the patient's history [2]. Social and economic importance of infection is determined by the outbreak nature of the disease, the need for quarantine measures, and the substantial material costs of treatment and rehabilitation of patients in case of development of moderate and severe degrees [3, 4]. An important epidemiological aspect of infection is also the possibility of development of its chronic form – shingles, it develops in 10–20% of patients who have already suffered chickenpox [5, 6].

The possible development of moderate and severe degree of disease in children requires the provision of emergency specialized medical care in hospital conditions with the duration of treatment of 21 days [7–10]. The long stay in hospital, the need for differential diagnosis and prevention of complications require the participation of an infection disease doctor, pediatrician, neurologist, ophthalmologist, otorhinolaryngologist in the treatment [11, 12]. In this situation, the solution of the issue of specific prevention of chickenpox tends to be possible and most rational [13–15].

The purpose of this study was to establish some aspects of the epidemic situation on chickenpox in Altai Krai and the city of Barnaul with justification of the need for vaccination of risk groups.

Materials and methods

The retrospective epidemiological analysis of the chickenpox incidence in the population of Altai Krai and Barnaul was carried out on the basis of statistical reporting forms No. 2 of the Federal State Statistical Monitoring "Information on infectious and parasitic diseases" for 2001–2018. Data processing was conducted using calculation of intensive and extensive indicators, calculation of arithmetic mean (X) and standard error of mean (m). The statistical analysis was carried out using Microsoft Excel.

Results and discussion

During the study period from 2001 to 2018, there was a tendency of increase in the chickenpox incidence among the Altai Krai population by 1.8 times from 346.15±0.11 $^{0}/_{0000}$ to 574.47±0.1 $^{0}/_{0000}$ ($p<0.01$). The population of Barnaul was also characterized by a tendency to increase in incidence rates by 1.13 times from 422.47±0.47 $^{0}/_{0000}$ to 515.28±0.13 $^{0}/_{0000}$. This situation was largely due to the increase in the number of officially registered cases of illness by medical organizations and was determined by the increase in the number of citizens' requests for medical assistance.

The maximum incidence rate both in Altai Krai and Barnaul was recorded in 2008 and amounted to 714.34±0.5 $^{0}/_{0000}$ and 1085.73±0.2 $^{0}/_{0000}$ respectively. The average long-term indicator in Altai Krai was 474.71±0.03 $^{0}/_{0000}$ and was lower than the same indicator in Barnaul (584.17±0.06 $^{0}/_{0000}$) by 1.2 times ($p>0.05$). The maximum incidence rates were recorded between December and February and averaged 75.14±0.01 $^{0}/_{0000}$, the minimum in August and averaged 13.2±0.03 $^{0}/_{0000}$ ($p<0.01$).

The average long-term incidence indicator among the adult population of Barnaul was 47.5±0.02 $^{0}/_{0000}$, which is 1.5 times higher than that in Altai Krai (31.5±0.14 $^{0}/_{0000}$) ($p<0.01$). Peak incidence was recorded in 2009 in Altai Krai (146.68±0.01 $^{0}/_{0000}$) and in 2008 – in Barnaul (55.87±0.11 $^{0}/_{0000}$). The average long-term incidence rate among children in Barnaul was 287.4±0.10 $^{0}/_{0000}$ and was higher than that in Altai Krai by 1.3 times (225.9±0.97 $^{0}/_{0000}$) ($p<0.01$).

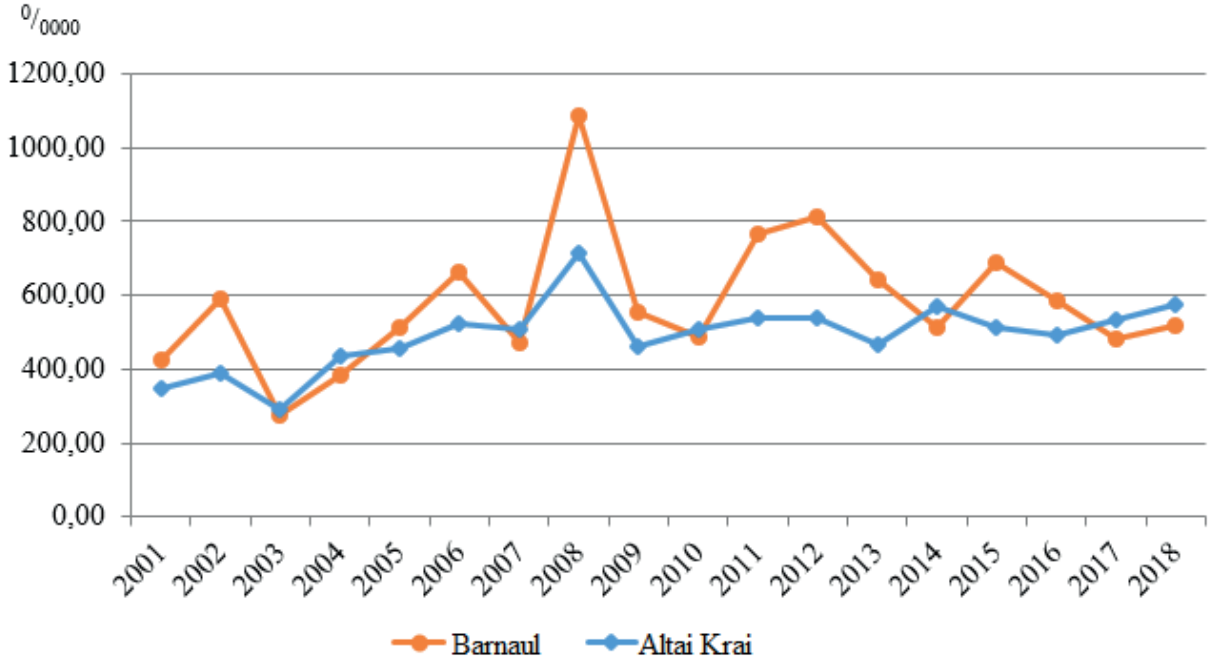

Figure 1. Dynamics of the chickenpox incidence in Altai Krai and Barnaul for 2001–2018 (per 100,000 population).

Children aged 3–6 years (53% and 62% respectively) and 7–14 years (29% and 19% respectively) represent the largest share in the structure of those infected with chickenpox in Altai Krai and Barnaul. The average long-term chickenpox incidence rate in Altai Krai among children aged 3–6 was 412.9±0.8 $^{0}/_{0000}$ and was higher than the incidence rate in children: 1-2 years – by 2.5 times (161.6±0.3 $^{0}/_{0000}$), 7–14 years – 2.8 times (148.1±0.4 $^{0}/_{0000}$), up to 1 year – 4.8 times (85.5±0.9 $^{0}/_{0000}$), and 15–17 years – 7.5 times (55.1±0.6 $^{0}/_{0000}$) ($p \leq 0.05$).

In Barnaul, the average long-term chickenpox incidence rate among children aged 3–6 was 755.1±0.03 $^{0}/_{0000}$ and was higher than the incidence rate in children: 1-2 years — 2.5 times (300.9±0.1 $^{0}/_{0000}$), up to 1 year – 5.4 times (140.0±0.8 $^{0}/_{0000}$), 7–14 years – 6.2 times (122.4±0.2 $^{0}/_{0000}$), and 15–17 years – 16.8 times (45.0±0.5 $^{0}/_{0000}$) ($p \leq 0.05$).

In the structure of the infected with chickenpox, the share of organized children in Altai Krai and Barnaul accounted for 48% and 59% respectively. Schoolchildren accounted for 33% and 22% respectively, unorganized children – 19% each. The results show that higher incidence rates were due to outbreaks in children's organized groups. This situation is due to the high contagiousness of the infection and the spread of the disease among persons who have not had a history of infection or vaccination (Figure 2a, b).

Currently, in Altai Krai in a number of cases, molecular biological studies of isolated vesicles for the varicella-zoster virus are used as special methods for determining the pathogen and confirming the diagnosis, as well as the determination of IgM, IgG antibodies to the virus of chickenpox in the blood. The necessity of using these methods in cases of moderate and severe forms of infection in children to prevent the development of possible complications is shown. Also in connection with the possibility of the chickenpox manifestation in the inapparent form, the diagnosis is based on the results of laboratory studies.

Currently, leucosis, cancer, HIV infection, immunosuppressive therapy and corticosteroids treatment are among the main risk factors for the development of severe course of the disease. Pregnant women are also at risk because transplacental transmission of the virus from an ill mother to a child is possible. At the same time, cases of chickenpox in a newborn to 11 day of life will be recognized as a congenital infection.

Congenital forms of infection include congenital chickenpox syndrome and neonatal chickenpox. During the first 20 weeks of pregnancy, intrauterine infection of the fetus can provoke spontaneous miscarriage, birth of a child with congenital chickenpox syndrome, or intrauterine death of the fetus. Neonatal chickenpox can develop in the case of an illness of a pregnant woman less than 10 days before childbirth. The timing of infection will determine the severity of the course of neonatal chickenpox. In this regard, vaccination in pregnancy planning is one of the key preventive measures to reduce the number of moderate and severe forms of disease in newborns.

Conclusion

The results obtained in the retrospective epidemiological analysis of the chickenpox incidence allowed to determine that in the structure of patients both in Barnaul and Altai Krai children aged 3–6 years made the main share. This category of chil-

dren is characterized by a predominant absence of a history of the disease and, as a rule, by a lack of vaccination. The possible development of moderate and severe forms of infection in newborns infected by transplacental transmission is also one of the factors determining the need for vaccination against chickenpox.

Conflict of interest. The authors declare no conflict of interest.

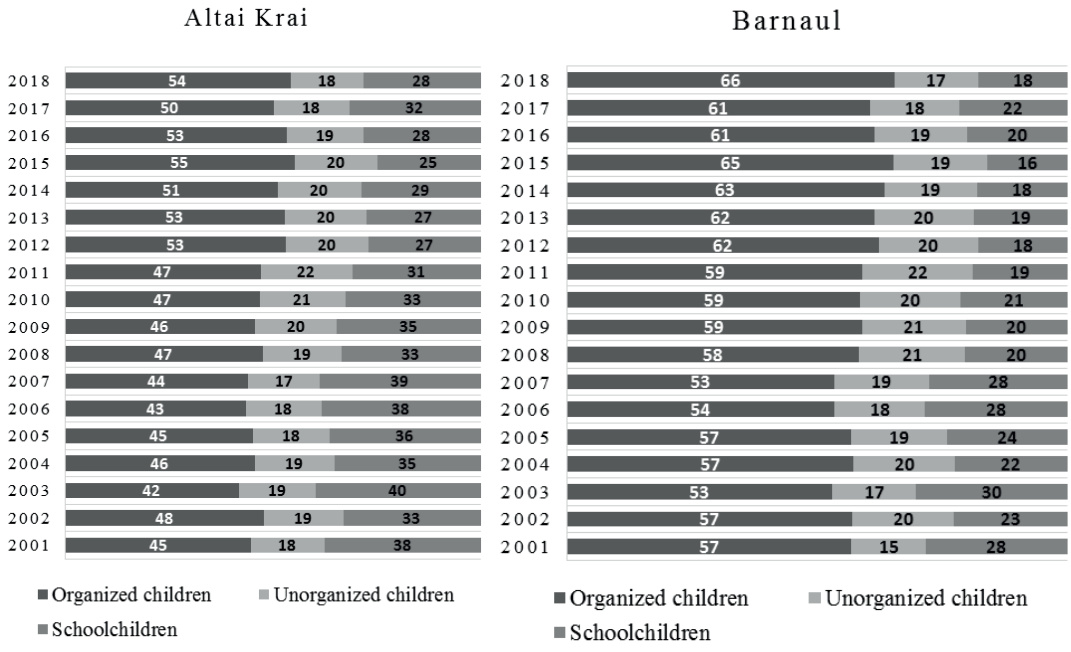

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Figure 2 (a, b). Structure of children under 17 with chickenpox by groups in Altai Krai and Barnaul for 2001–2018 (%).

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MODERN VIEW ON THE PATHOGENESIS OF NSAID-INDUCED GASTROPATHY

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The review analyzes modern research data on the factors, causes and mechanisms of development of NSAID-induced injury of the gastric mucosa. The role of prostaglandins, nitrogen oxide, free radical oxidation, and apoptosis processes in protection and damage of the gastric mucosa was studied. On the basis of collected data, a new vector of development of effective schemes of pharmacological correction of NSAID-induced gastropathy was proposed.
Key words: *NSAID gastropathy, prostaglandins, oxidative stress, apoptosis, gastric mucosa.*

According to the Federal State Statistics Service of the Russian Federation, the incidence of various pathologies of the digestive organs is about 34/1000 people of the population, and over the past 10 years, it remains approximately at the same level, without a downward trend [1]. Gastropathy caused by taking nonsteroidal anti-inflammatory drugs (NSAIDs-induced gastropathy) plays an important role in that respect. This term describes the damage to the upper gastrointestinal mucosa with the formation of erosions and ulcers, detected during endoscopic examination. The use of NSAIDs is the second major cause of gastric mucosal erosion after Helicobacter Pylori infection [2, 3]. At the same time, the incidence of H. pylori-associated peptic ulcer disease in the EU, USA, Japan, and other countries is gradually decreasing, while NSAID-induced gastropathy is becoming more common and is now increasingly firmly established as the main non-infectious etiological factor in the development of gastric ulcer [4-6].

To date, there has been proved a close correlation between the epidemiology of gastric ulcer and gastritis and the incidence of rheumatoid arthritis, arthrosis, and other inflammatory diseases, the pharmacotherapy of which requires long-term administration of NSAIDs. [6-9]. At the same time, it was found that 40-50% of all acute gastrointestinal (GI) bleeding requiring endoscopic or surgical intervention was caused by the intake of NSAIDs [10-13]. With total mortality from these complications about 10%, among these people, patients receiving NSAIDS are 2-3 times more likely to appear than those not receiving drugs of this group [14-19].

At the same time, the application of NSAIDs is so important that it is not possible to exclude or at least limit the use of these drugs in the foreseeable future. In addition, the mechanism of the ulcerogenic action of NSAIDs is known to be almost identical to the main mechanism of anti-inflammatory, antipyretic and analgesic action of NSAIDs, resulting in the inhibition of cyclooxygenase (COX) and prostaglandin synthesis disruption [20-22]. This means that any medical use of NSAIDs, especially of non-selective action on COX-1,2, may and will cause the development of gastropathy. This problem was solved to a certain extent by creating NSAIDs – selective COX-2 inhibitors [23-25]. However, it turned out that these drugs produce weaker pharmacological effects than non-selective COX-1,2 inhibitors, which therefore remain the most commonly used drugs.

Thus, despite significant progress in the approach to the rational use of NSAIDs, the risk of adverse events from the gastrointestinal tract when taking these drugs is still high. In this regard, the question of finding new effective and safe pharmacological agents for the prevention of NSAID-induced gastropathy is still of present interest.

The spectrum of drugs used for the treatment and prevention of NSAID-gastropathy is wide and includes antacids, bismuth preparations, prostaglandin analogues, antisecretory drugs (H2-blockers, proton pump inhibitors) [26]. However, therapy with these groups of drugs is not yet adequate, frequently because of side effects.

Given the fact that the inhibition of COX and reduction of endogenous prostaglandin synthesis occupy a leading position among the mechanisms of the damaging effect of NSAIDs, the use of exogenous prostaglandins is suitable for the prophylaxis of damage.

The synthetic analogue of prostaglandin E1, misoprostol, based on the results of a large meta-analysis, demonstrated efficacy in the prevention of gastric ulcers (74%) and duodenal ulcers (53%) compared to placebo [27]. The frequency of serious gastrointestinal complications in patients receiving NSAIDs in combination with 800 μg of misoprostol was 0.76% compared with 1.5% in the placebo group, where gastrointestinal perforation, the most dangerous pathology, occurred 10 times less frequently in patients receiving misoprostol than in control [28]. Misoprostol is effective in stimulating bicarbonate and mucus production, maintaining adequate local blood flow and mucosal integrity as protective barriers. In response to damage, misoprostol stimulates mucosal epithelial proliferation [29].

Unfortunately, the clinical benefit of misoprostol is limited mainly to its gastrointestinal side effects such as cramps, abdominal pain, and diarrhoea, as well as non-gastrointestinal side effects (an increase of contractile activity of the myometrium; systemic vasoplegia: hypotension, facial hyperemia, headaches) [30].

Currently, antisecretory drugs such as H2 blockers and proton-pump inhibitors (PPIs) obtain a central place in the treatment and prevention of NSAID gastropathy [26, 31].

At the same time, many studies comparing these two main groups of drugs confirm that H2 blockers (ranitidine, famotidine) are not effective enough in the treatment of NSAID-induced gastropathy. PPI drugs (omeprazole) show the highest therapeutic activity both in the treatment and in the prevention of pathology [32-35; 31].

They provide a more powerful and prolonged inhibition of gastric acid secretion, a higher healing rate, and symptomatic relief and are recommended as initial therapy for most patients. According to a meta-analysis of randomized controlled trials (RCTs), proton-pump inhibitors compared to H2 receptor blockers systematically show better results [19, 36, 37]. According to the OMNIUM (OMEPRAZOLE VERSUS MISOPROSTOL FOR NSAID-INDUCED ULCER MANAGEMENT) study, it was possible to maintain remission with taking NSAIDs for 6 months with the appointment of omeprazole in 61% of patients, and with the appointment of misoprostol in 48% of patients. Omeprazole was more effective than ranitidine in preventing NSAID gastropathy, according to the ASTRONAUT (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment) study [38, 39].

Despite its high efficacy, the PPI group cannot be considered ideal for the prevention and treatment of NSAID-induced gastropathy. In recent decades, adverse events caused by prolonged use of this group have been increasingly reported.

First, these drugs do not sufficiently protect the intestinal mucosa. One study demonstrated that 68% of patients experience intestinal membrane damage 2 weeks after oral administration of NSAIDs in combination with PPIs [40]. Because the pH in the stomach is very low, PPIs are effective treatments for NSAID-induced gastric ulcers [38]. However, these drugs lose their efficacy as the pH is about 8. In the intestine, NSAIDs reduce ATP production in the mitochondria of intestinal epithelial cells; therefore, membrane permeability is increased by the resulting disturbance to the maintenance system in the junction between the cells [41]. Intestinal bacteria, bile acids, and proteolytic enzymes thus reach the cell membrane, leading to migration and activation of neutrophils. Activated neutrophils produce cytokines or nitric oxide (NO), which causes damage to intestinal membranes [42].

Second, and more importantly, one of the limitations, often encountered in the literature, is the information that PPIs can alter the composition of the intestinal microbiome, which even exacerbates NSAID-induced damage to the small intestine [43-45]. A meta-analysis published in 2013 evaluating the association between intake of PPIs and small intestinal bacterial overgrowth (SIBO) among patients concluded that the use of PPIs was statistically associated with the risk of developing SIBO. Presumably, this effect may be associated with chronic acid suppression and resulting hypochlorhydria, which is a direct consequence of the mechanism of PPI action [46].

Thus, modern methods of therapy and prevention of NSAID-induced gastropathy can hardly be called perfect. There are still a number of unresolved problems associated with insufficient effectiveness or adverse reactions to therapy, respectively, the question of finding the optimal means of protection is not yet closed.

The essence of the problem of effective and safe prevention of NSAID-induced gastropathy is that there are no drugs that effectively suppress the development of erosive lesions without affecting the intestinal secretory and contractile functions in therapeutic practice at the moment. In order to establish the most effective mechanism for preventing the ulcerogenic action of NSAIDs, it is necessary to thoroughly understand the pathogenesis of this type of gastropathy. Only with a deep understanding of the mechanisms involved in the pathology, it is possible to develop schemes that effectively prevent the damaging effect, but do not inhibit the necessary functions for normal digestion of the gastrointestinal tract.

Protective factors of the gastric mucosa

General protection mechanisms

It is known that the erosions in the gastric mucosa occur when the balance between aggressive and protective factors is shifted towards aggressive. The main sources of gastric mucosal damage are acid-peptic activities, fibrous and harsh chemical components of food, poisons and toxic drugs, as well as pathogenic bacteria and their products (H. pylori, streptococci, staphylococci, fungi of the genus Candida, etc.) [47].

The gastric protective mechanisms can be separated into three main categories: pre-epithelial, epithelial, and post-epithelial [48, 49].

Pre-epithelial protective mechanism consists mainly of the mucus layer, which contains mucus, bicarbonate and surfactant phospholipids and prevents contact of epithelial cells with luminal noxious agents such as gastric acid. Mucus is a water-insoluble gel composed of glycoprotein polymers closely adherent to the surface of epithelial cells. It includes IgA, lysozyme, lactoferrin and

other components. The mucus layer protects the gastric mucosa from physical and chemical factors, from the action of hydrochloric acid and pepsin, bacteria, viruses and their toxins [50]. The bicarbonate secretion reduces the aggressive properties of hydrochloric acid and increases the pH of the protective mucus layer. Mucus and bicarbonates are secreted by gastric epithelial cells (namely surface mucoid cells). As a result, the pH on the surface of the epithelial cells of the gastric mucosa is usually maintained in the neutral range when the pH of the gastric lumen reaches 1-2.

The surface epithelial cells themselves serve as a second line of protection. Their dense junctional complexes limit the diffusion of hydrogen ions, they are responsible for the secretion of mucus and bicarbonate, and have the ability to migrate to the site of damage to repair the damaged region (restitution).

Microcirculation in the mucus membrane of the gastric submucosal layer is one of the most important post-epithelial defense mechanisms. Blood flow provides a sufficient supply of micronutrients and oxygen to ensure the adequate functioning of epithelial cells and sufficient mucus and bicarbonate secretion. In addition, the protective function is to remove acid and other toxic by-products of metabolism. By facilitating acid removal, increased microcirculatory blood flow prevents the accumulation of harmful H+ ion concentration in the tissue and limits acid damage to the mucosal surface [51].

The role of nitric oxide

One of the important post-epithelial protective factors is nitric oxide (NO). NO is synthesized by the enzyme NO synthase (NOS), which converts L-arginine (L-Arg) into L-citrulline (L-Cit) with the release of nitric oxide. The enzyme in the body is found in three isoforms: endothelial (eNOS), neuronal (nNOS) and inducible (iNOS) [52, 53]. eNOS and nNOS are expressed under normal conditions by endothelial cells and neurons, respectively, and perform a number of important homeostasis-supporting functions, such as vasoprotection, maintaining adequate microcirculation, optimizing neurotransmission, and maintaining neuroplasticity [54].

Nitric oxide through activation of guanylate cyclase and the accumulation of a secondary mediator cyclic guanosine monophosphate is involved in many protective processes in the gastric mucosa: stimulation of protective mucus production, angiogenesis, regeneration of damaged gastric mucosal areas [55]. Anti-aggregating, vasodilating, anticoagulant factors are its final effects.

iNOS, not secreted under normal conditions, is expressed to a greater extent by macrophages and neutrophils under appropriate conditions associated with inflammation [56]. With a high iNOS expression or eNOS dissociation during biochemical reactions, instead of the form of NO, active nitrogen forms may begin to accumulate, for example, peroxynitrite ($ONOO^-$) [57]. It is a very active oxidative radical that participates in lipid modification, damages DNA, suppresses enzyme function, etc. The formation of active forms of nitrogen is an adverse event that can consolidate pathological mechanisms of ulcers.

The damaging effect of aggressive factors to varying degrees weakens the effectiveness of the above protective mechanisms, and it is important to understand their role in determining the pathogenetic mechanisms of gastropathy. In particular, it is under the influence of drugs and life products of microorganisms that the activity of protective factors can decrease, and in this case, the regeneration of the mucosa becomes insufficient, so the erosive damage develops.

The role of prostaglandins

For the first time, the protective role of prostaglandins (PG) in the gastric mucosa was shown by A. Robert in 1979 [115]. Scientists have discovered the protective effect of prostaglandin E2 in the gastric mucosa of rats with gastropathy induced by various toxicants [10]. Thus, they proposed the concept of "cytoprotection", which implied the protection of mucous cells from damage without significant reduction of acid secretion.

The exchange of prostaglandins in the cells of the gastric mucosa is sequentially catalyzed by several enzymes. The first stage of synthesis of arachidonic acid occurs under the action of the so-called PG H_2 synthase, which has two catalytic centers: cyclooxygenase and peroxidase.

It is known that cyclooxygenase exists in two isoforms: COX-1 and COX-2. Although both isoforms catalyze the same reactions, COX-1 is a constitutive enzyme in most cells: it is synthesized and active in the basal state; the activity level of COX-1 does not change significantly during cell growth and development. At the same time, COX-2 is usually present in tissues in small quantities and is significantly induced by cytokines, growth factors and other stimulants during an inflammatory reaction [58, 59]. To some extent, the eicosanoids produced by COX-1 participate in the implementation of basic functions, such as mucus secretion to protect the gastric mucosa, hemostasis and maintenance of kidney function, while synthesized COX-2 lead to inflammatory and other pathological changes [60]. However, the separation of COX isoforms into "physiological" and "pathological" is not quite correct, both of these enzymes can participate in the protective functions of the body. For example, COX-1 is primarily responsible for the production of constitutive endogenous PGs involved in the protection of the mucous membrane, whereas COX-2 is primarily responsible for those

involved in the healing of already emerging gastric or small intestine ulcers [61, 62].

Cyclooxygenases catalyze the transformation of arachidonic acid into an unstable PGG_2 compound, which is subsequently converted by peroxidase to PG H_2. Then, under the action of a number of PG-metabolizing enzymes (synthetases), the initial compound is transformed into PGE2, 6-keto PGF 1α, thromboxane B 2, PGF 2α, and PGD 2.

PGE2 plays a key role in maintaining the integrity of the mucous membrane. Its functional activity is mediated through receptors associated with G-protein, which is divided into 4 specific subtypes: EP1-EP4, and their distribution explains the multiple effects of this prostanoid.

The stimulation of EP1 receptors associated with Gq-protein causes the activation of phospholipase C (PLCβ) followed by the accumulation of inositol triphosphate (IP3) and diacylglycerol (DAG). These secondary mediators release calcium ions into cytosol, resulting in activating effects. EP2, EP4 receptors, being associated with Gs-protein, activate adenylate cyclase, which is responsible for the accumulation of another secondary messenger – cAMP, which performs relaxing effects through cAMP-dependent protein kinase A. EP3 receptors associated with Gi-protein inhibit adenylate cyclase, performing the opposite effects.

Endogenous prostaglandins play a role in regulating various functions of the stomach, such as acid and gastric secretion, mucus and bicarbonate secretion, blood supply and maintaining the integrity of the mucous membrane, which promotes cytoprotection of the stomach [63]. According to studies, PGE2 inhibits acid secretion through EP3 receptors and increases mucus and bicarbonate secretion in the stomach through EP4 and EP1 receptors [64-69]. In cold stress, as well as ischemia accompanied by reperfusion, cytoprotection is mainly caused by PGI2 via IP and partly EP4 receptors. PGI2 supports microcirculation in the mucous membrane and reduces gastric secretion of acid and gastrin less effectively than PGE2.

PGE2 also shows a protective effect against acid damage to the duodenum and indomethacin-induced small intestine lesions through the stimulation of EP3/EP4 receptors. These effects in the stomach and duodenum are functionally related to gastric contraction inhibition (EP1), stimulation of duodenal secretion of HCO3- (EP3/EP4), and suppression of bacterial invasion due to inhibition of gastrointestinal motility (EP4), as well as stimulation of mucus secretion (EP3/EP4). In addition, PGE2 has a healing effect on the erosion of the stomach and the small intestine through increased expression of the vascular endothelial growth factor (VEGF) and stimulation of angiogenesis through EP4 receptor activation. It is important that EP1 receptors and their regulation of gastric musculature tone, according to modern ideas, play a leading role in the protective function of prostaglandins [39].

A very important part of the protective effect of prostaglandins is their effectiveness in relation to the tone and permeability of the vessels. In particular, prostacycline (PGI2) is a powerful vasodilator and antiaggregant. Prostacycline reduces the content of calcium ions in cells by accumulating a secondary messenger – cyclic adenosine monophosphate. PGE2 has a vasodilatory effect as well, and PGF2a is mostly responsible for the vasoconstriction of large vessels and dilatation of small vessels [60, 70, 71]. In general, the balance of the processes of vasoconstriction and vasodilatation supports normal microcirculation of the mucosa, ensuring sufficient rate of epithelium regeneration, thereby fulfilling the protective function.

Prostaglandins play a key role in protecting the epithelium of the stomach, strengthening the preepithelial, epithelial, post-epithelial protective mechanisms: regulate the secretion of bicarbonate and mucus, inhibit the secretion of gastric acid and play an important role in maintaining the regeneration of epithelial cells and mucous membrane blood flow [72]. That is why medications capable of inhibiting their synthesis show such high toxicity towards GM.

Pathogenetic mechanisms of NSAID-induced gastropathy

It has been repeatedly shown that chronic NSAIDs intake leads to a significant increase in the risk of ulcerative lesions of the gastrointestinal mucosa [72–74]. Summarizing the general pathogenetic mechanisms of the damaging effect of NSAIDs on the mucosa of the digestive organs, it is necessary to allocate: 1) the main way – blocking the production of prostaglandins E2 and I2 (through COX); 2) the way due to the main and other mechanisms: reduction of gastric mucus and bicarbonate production, reduction of blood flow in the gastric mucosa, reduction of platelet aggregation, increase of hydrochloric acid and pepsinogen production, increase of formation of free radicals and reduction of glutathione formation, stimulation of neutrophils chemotaxis, increase of tumor necrosis factor, increase of synthesis of leukotrienes B4 toxic for the gastric mucosa, change of intracellular calcium content, dissolution of oxidative phosphorylation, inhibition of NO synthesis, which causes circulatory disorders and adhesion of leukocytes to vascular endothelium in the gastric mucosa, stimulation of apoptosis of epithelial cells [75].

Cell targets for non-COX-mediated NSAIDs are cGMP phosphodiesterase, peroxisome proliferator-activated receptors, Retinoid X receptor (regulation of lipid metabolism), IKKβ, AMP kinase, etc. [75–78]. It is also proved that harmful physiological damage occurs as a result of decreased blood flow in the stomach and mild ischemia caused by the

gastric mucosa. Adequate blood flow can have a pronounced protective effect on the mucous membrane of the gastrointestinal tract, preventing the development of experimental erosive damage of the gastroduodenal zone. Hypoxia of the mucous tissue, which occurs at blood flow violation, leads to deep hemorrhagic necrosis with the formation of erosions [79–81].

Cyclooxygenase pathway

The most important role in the mechanism of ulcerogenic action of NSAIDs is played by the inhibition of cyclooxygenase and, accordingly, the disruption of the metabolism of prostaglandins. It has been experimentally confirmed that NSAIDs cause lesions of the gastric mucosa at doses that can significantly reduce the level of PGE2 [21, 22]. Previously, it was believed that the inhibition of COX-1, the constitutive isoform of the enzyme, was responsible itself for the development of damage in the gastric mucosa. However, then studies confirmed that the suppression of the effects of the COX-1 type significantly increases the expression of the COX-2 genes [22]. This reaction is considered as an adaptive mechanism of protection of the mucosa from aggressive factors in conditions of suppression of normal protective functions. Accordingly, inhibition of two isoforms at the same time can bring much more pronounced harm to the mucous membrane of the stomach than inhibition of COX-1 separately [21].

According to meta-analysis of the results of studies of gastrotoxicity of various NSAIDs, indomethacin, a derivative of indoleacetic acid, is one of the drugs with a high probability of gastroduodenal complications development [116]. Indomethacin is a reversible non-selective COX inhibitor, reversibly blocks both isoforms of the enzyme. This leads to a decrease in the concentration of prostaglandins, especially PGE2, in the gastric mucosa and a decrease in all protective functions, there is a decrease in the synthesis of mucus and bicarbonate, deterioration of blood flow of the mucous membrane, increased acid secretion, physicochemical damage of cell membranes [82, 83].

For all that, the fact of inhibition of prostaglandins synthesis is an important, but not the only sufficient factor for the development of erosion in the gastric mucosa [84–86]. In general, a whole range of mechanisms takes part in the development of this pathological effect.

The role of oxidative damage in the development of gastropathy. Disruption of mitochondrial metabolism

NSAID-induced mitochondrial oxidative stress (MOS) is considered to be an important prostaglandin-independent way of induction of gastric mucosa damage [77, 87, 88].

Mitochondria are membrane organelles of cells that perform a number of important functions. The structural and functional integrity of mitochondria is the basis for maintaining bioenergy homeostasis and cellular health. Constant dynamic equilibrium is important for mitochondria functions, including adenosine triphosphate (ATP) production, intracellular Ca2+ level regulation, endoplasmic reticulum buffering, and cell death due to apoptosis activation [88–91].

The mitochondrial respiratory chain is the main source of reactive oxygen species (ROS), which are mainly formed in complexes I and III of the respiratory chain. More importantly, the mitochondrial respiratory chain is one of the main targets for the destructive effects of ROS at the same time. NSAIDs dissolve mitochondrial oxidative phosphorylation, which reduces the concentration of intracellular ATP. This leads to the release of cytochrome from the mitochondrial intermembrane space into the cytosol and the release of ROS such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), thereby causing caspases activation and cell lipid peroxidation, all this leads to cellular apoptosis [60, 88, 92–96]. In addition, this change leads to the loss of intercellular integrity, as intercellular compounds are controlled by ATP-dependent actin myosin complexes and, as a consequence, the permeability and subsequent damage to the mucous membrane increase [72]. The damaging effect also reduces the proliferation of GM cells [9].

In a study published in April 2019, it was shown that indomethacin shifts mitochondria dynamics towards increased fission, which induces the bioenergy crisis and then causes apoptosis of rat gastric mucosa cells in vivo [9].

To be more precise about the mechanisms of proapoptotic action, it is shown that one of the pathways activated by indomethacin is the pathway of protein kinase C-zeta (PKCζ)-p38 MAPK-dynamin-dependent protein 1, which is an activator of mitochondrial fission. As a result of the detected mechanism, indomethacin caused a violation of metabolic parameters of mitochondria: reduced basal respiration, significantly reduced ATP production, and lost cell reserves. These disorders gradually led to mitochondria depolarization and induction of cell apoptosis, which increased within 24 hours after administration.

An important issue in this process is the possibility of forming a closed cycle: excess ROS production reduces the potential of the mitochondrial membrane, which is why the normal course of biochemical reactions is disturbed, new excess amounts of ROS are released from mitochondria, which destroy mitochondria membranes [97-98].

Autophagy as a mechanism of cell death under the influence of indomethacin

One of the important mechanisms of cell protection against apoptosis is macroautophagy (autoph-

agy). This process is activated in case of damage to epithelium cells by aggressive factors, in particular, autophagy plays an important role in maintaining cell homeostasis during nutrient deprivation, oxidative stress or endoplasmic reticulum stress [99]. The purpose of autophagy is to destroy excess and damaged organelles, cytosolic proteins and invasive microorganisms inside the cell. Autophagy usually processes macromolecular aggregates resulting from pathways of oxidative stress and the mitochondrial production of ROS may also reduce by recycling old and damaged mitochondria [100]. Thus, autophagy is believed to be an important cellular antioxidant mechanism [101].

This process is coded by genes associated with autophagy (Atg) and includes: formation and prolongation of the insulating membrane, formation of a two-membrane sequestrating compartment called phagophore, which turns into the autophagosome (merging with lysosome) [102]. Once the particle is delivered to the lysosome and decomposed, the resulting macromolecules (or small molecules) are released back into the cytosol and used as components for building new macromolecules and energy sources to maintain the vitality of cells, which is the dominant role of autophagy [103]. However, it is believed that excessive autophagy may also be involved in cell death [104].

The data obtained in the course of studies on the influence of indomethacin on the autophagy process are ambiguous. On the one hand, a number of studies report that the autophagy inhibition by pharmacological or genetic means protects cells from cytotoxicity of indomethacin, resulting in a the assumption that indomethacin causes damage by stimulating excessive autophagy [40, 97, 105].

On the other hand, there is evidence in the literature showing that indomethacin inhibits the process of autophagic degradation [106]. A study in 2018 showed that the drug violated the lysosomal function, increasing the permeability of the lysosomal membranes. It was also found that by increasing the lysosomal pH, indomethacin inhibited the activity of acid lysosomal enzymes. However, the assumption of autophagy inhibition is more likely to apply to altered cells (neoplasias) of the stomach, and the data indicating the activation of the process are more extensive.

It is interesting that, as mentioned earlier, autophagy can occur in response to mitochondrial oxidative stress, as well as to the stress of endoplasmic reticulum. Thus, these mechanisms can be both consistent and parallel links of pathogenesis of NSAID-induced gastropathy. Indeed, there are studies that have found the relationship between these types of stress and autophagy activation [97, 106]. It has been proved that these stressful effects and the accumulation of active oxygen forms inside the cells under the influence of indomethacin provoke Atg phosphorylation and autophagy in the cells of the intestine mucous membrane, which suggests the presence of the same cause-effect relationship of processes in the stomach tissue [97, 106].

Other mechanisms of damaging action

Discussing the mechanisms of PG-independent indomethacin damage, another discovered path of its harmful effect on the mucous membrane should be noted. Change of redox homeostasis activates the alarm of nuclear factor-kB (NF-kB), which is associated with proinflammatory tissue damage [107]. NF-kB is a nuclear protein, one of the most important apoptosis suppressors. NF-kB regulates the expression of more than 400 genes, many of which are critical to cell survival [108]. When activation preventing or inhibiting this factor, several apoptosis mechanisms are triggered, including the mitochondrial pathway through the release of cytochrome C and the activation of caspase-3. The expression of a number of apoptosis protein-inhibitors and caspase inhibitors decreases [78].

Indomethacin, having an acidic nature (pKa=4.5), in the acidic environment of the stomach remains non-ionized and can penetrate into cells [109]. In cell cytoplasm (pH 7.1), the molecule ionizes and loses its ability to diffuse. Accumulation of drug ions inside cells aggravates gastrotoxicity [60]. Thus, there is an induction of local reverse diffusion of H+ ions into the gastric mucosa, the normal acid alkaline balance in the cells is disturbed, tissue acidosis and cell damage occur [82].

The role of increased muscle contraction in the pathogenic mechanism of indomethacin-induced gastric ulceration was also demonstrated [110–112]. W.A. Mersereau and E.J. Hinchey [111] were the first to demonstrate the importance of hypermobility of the stomach and folds of mucosa in the genesis of gastric lesions in response to NSAIDs. A group of Japanese scientists reported that indomethacin in an ulcerogenic dose increases the gastric motor activity and causes microcirculatory disorders due to pathological compression of the mucous membrane of the gastric wall [112-113]. Experimentally, the importance of this element was demonstrated as follows: when indomethacin was administered at a low dose capable of inhibiting PG synthesis, the drug showed more than 90% of inhibition of PG mucous membrane generation, but the method itself did not cause any stomach damage. At the same time, when indomethacin was administered in combination with 2-deoxy-D-glucose (agent causing hypermobility of the gastric wall), the administration provoked severe lesions in the stomach. Thus, scientists have come to the conclusion that PG deficiency can be crucial in increasing the susceptibility of the mucous membrane to damage against the background of hypermobility [86].

The effect of indomethacin on the contractive activity of the stomach seems particularly import-

ant against the background of the detected pattern: in one experiment, stomach acidity inhibitors did not protect the gastric mucosa from damage in the presence of exogenous acid, unlike atropine, which reduced stomach peristalsis and prevented the formation of erosion even in the presence of exogenous acid [110].

Conclusion

The fact that the lack of prostaglandins plays the main role in the development of NSAID-induced gastropathy remains indisputable and is confirmed by many experimental data. However, the lack of prostaglandins alone is not the only factor that causes erosive damage to GM. In addition to inhibiting cyclooxygenase, indomethacin has a multifaceted damaging effect on the course of oxidative processes in mitochondria, resulting in the accumulation of toxic products, fragmentation of mitochondria, and eventually cell apoptosis. Moreover, oxidative stress is also inextricably linked to the activation of autophagy as a separate mechanism for cell protection, but in case of pathology leading to their death. In this regard, the role of mitochondrial oxidative stress in the pathogenesis of NSAID-induced gastropathy is significant and, as knowledge deepens, becomes increasingly important in understanding the mechanisms of damaging action on the mucous.

It has been proved that the acute phase of gastric mucosa damage includes inflammatory reactions and oxidation imbalance, in which there is up-regulation of proinflammatory cytokines, such as tumour necrosis factor α (TNF-a) and interleukins (IL-1β and IL-6), migration of neutrophils and mononuclear cells, and generation of free radicals [117-118]. Therefore, today the relevant opinion is that therapeutic targets in erosive processes in the stomach should not be limited to control acid secretion, but also include control of inflammatory reactions and regulation of unbalanced oxidation [114].

Given the need of modern society for effective and, most importantly, safe prevention of NSAID-gastropathy, only such a remedy can become a potentially ideal drug for this purpose, which does not inhibit the basic digestive functions of the stomach, but at the same time promotes more effective protection of the mucosa, reduces the severity of oxidative stress, normalizes the processes of apoptosis and autophagy in GM cells.

Conflict of interest. The authors declare no conflict of interest.

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EFFECT OF ACUTE GENERAL PRENATAL HYPOXIC HYPOXIA ON THE SYSTEM OF MATRIX METALLOPROTEINASES OF THE RABBIT FETUS ON THE 27-28TH DAY OF PREGNANCY

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The influence of hypoxic hypoxia on the concentration of matrix metalloproteinase-1 (MMP-1), the concentration of tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) in amniotic fluid (AF) of rabbits on the 27-28th day of pregnancy was studied. The rabbits were divided into two groups: experimental (n=9) and control (n=6). Rabbits of the experimental group were placed in a hypoxic chamber containing 10±2% of oxygen and 90±2% of nitrogen for 1 hour, after which they were killed, and the amniotic fluid (experiment – n=35, control – n=35) was taken from fetuses. The results are presented in the form of a median (25–75%). Acute general hypoxic hypoxia increased the concentration of MMP-1 in AF [experience – 2.14 (2.03–2.29) ng/ml, control – 1.18 (0.98–1.38) ng/ml, p=0.019], increased the concentration of TIMP-1 in AF [experience – 1.96 (1.80–2.09) ng/ml, control – 1.74 (1.61–1.88) ng/ml, p<0.001] and MMP-1/TIMP-1 ratio in AF [experience – 1.10 (1.02–1.18), control – 0.70 (0.58–0.83), p<0.001]. Conclusion: acute general hypoxic hypoxia in late pregnancy causes changes in the biochemical composition of AF, characterized by an imbalance between the levels of MMP-1 and TIMP-1, which indicates the activation of the system of matrix metalloproteinases of the fetus.

Key words: *hypoxia, prenatal period, amniotic fluid, MMP-1, TIMP-1.*

The perinatal period includes prenatal (pre-delivery), intranatal and early neonatal periods. Perinatal hypoxia (PH) is one of the leading causes of child mortality and morbidity. Among the factors causing damage in perinatal hypoxia, the activation of the system of matrix metalloproteinases – Zn-containing extracellular proteases can be emphasized [1]. On the other hand, prenatal hypoxia is associated with an increased incidence of premature birth, which is often caused by rupture of amniotic membranes with discharge of amniotic fluid and premature activation of labor activity [2]. The most significant regulators of MMP activity are tissue inhibitors of matrix metalloproteinases (TIMP), the most universal of which is TIMP-1 [3]. The research objective was to study the effect of general hypoxic hypoxia on the key components of the system of matrix metalloproteinases (MMP-1 and TIMP-1) in amniotic fluid.

Materials and methods

Subject of research. The study was carried out on the first pregnant rabbits (n=15) weighing 4-5 kg at the period of pregnancy of 27-28 days (with normal duration of pregnancy of 31 days). Fertilization was carried out by different randomly chosen males, after which female rabbits were in single cells on free food. The rabbits were randomly divided into two groups: experimental (n=9) and control (n=6).

General acute hypoxic hypoxia. Rabbits from the experimental group were placed in an individual hermetic flow chamber for 60 minutes, where the compressor injected a gas mixture containing 10±2% of oxygen and 90±2% of nitrogen. The control of gas composition in the chamber was carried out by means of gas analyzer Microlux O_2+CO_2 (OOO "Microlux", Yekaterinburg, Russia). The rabbits from the control group were placed in the same chamber containing ambient air for 60 minutes.

Obtaining samples of amniotic fluid. Animals were killed by cervical dislocation, after 15 minutes, the midline laparotomy was carried out and the uterus was removed. Amniotic sacs with fetus were isolated and extracted from the uterine cavity, the maternal and fetal parts of the placenta were separated without disturbing the integrity of the amniotic sac. Amniotic fluid was extracted from the amniotic sac with a disposable syringe. The general characteristics of the fetuses are presented in Table 1. Samples of amniotic fluid were centrifuged for 15 minutes at 1200 g, frozen and stored at −20°C for no more than one month prior to the biochemical study.

Biochemical studies. The concentration of MMP-1 in the amniotic fluid of rabbits was determined using the enzyme immunoassay kit Elabscience® Rabbit MMP-1 (Matrix Metalloproteinase 1) ELISA Kit (cat. No. E-EL-RB0349, Elabscience, USA). The concentration of TIMP-1 in the amniotic fluid of rabbits was determined using the enzyme immunoassay kit LSBio Rabbit TIMP1 ELISA Kit (Sandwich ELISA) (cat. No. LS-F5382, LSBio, USA). The optical density of the reaction mixture was measured using a vertical photometer Multiscan (Labsystem, Finland).

Table 1

Weight of the fetus and placenta on 27-28 days of life

	Hypoxic hypoxia (n=35)	Control (n=35)	P
Weight of the fetus, g	36.7 (28.8–42.3)	39.6 (31.0–44.3)	0.388
Weight of the fetal part of the placenta, g	3.14 (2.70–3.72)	3.47 (3.12–3.90)	0.144

Note: data are presented in the form of median (25–75%), P is the significance of cross-group differences according to the Mann–Whitney U-test.

The *statistical analysis* of data was carried out in the program JMP 7.0 (SAS Institute, USA). We calculated the median, 25 and 75 percentiles, the reliability of inter-group differences according to the Mann–Whitney U-test, multiple correlation analysis by the Spearman criterion. The statistical significance level was taken as 5% ($p<0.05$).

This work is approved by the local ethical committee of FSBEI HE ASMU of the Ministry of Health of the Russian Federation.

Results and discussion

Matrix metalloproteinases are involved in various physiological (growth, development, differentiation of cells) and pathological processes (inflammation, metastasis of tumors) [4]. Through proteolysis of matrix metalloproteinases substrates (components of extracellular matrix – collagen, fibronectin, proteoglycans) and extracellular domains of membrane receptors of cells, these enzymes actively affect intercellular communications regulating the stability of the extracellular matrix, the release of cytokines deposited in the extracellular matrix, and the sensitivity of membrane receptors to extracellular mediators. The mechanism of regulation of matrix metalloproteinases is realized through the action of their specialized TIMP inhibitors blocking the active center of the enzyme [3], partial proteolysis, including autoactivation [5] and deposition in the extracellular matrix [6].

An important factor of premature labor is the activation of matrix metalloproteinases system, as it causes the destruction of fetal membranes, violation of the integrity of the fetal bladder with discharge of amniotic fluid and enhancement of labor activity. It is noteworthy that premature labor activity is often associated with fetal suffering from hypoxia [2]. At the same time, the relationship between hypoxia and activation of the fetal matrix metalloproteinases system has little evidence.

Acute general prenatal hypoxic hypoxia in rabbits on the 27-28th day of pregnancy caused an increase in the concentration of MMP-1 by 81.4% and an increase in the concentration of TIMP-1 by 12.6%, which together with the increase in ratio of concentrations MMP-1/TIMP-1 from 0.7 to 1.10 indicates the activation of matrix metalloproteinases system in amniotic fluid in acute general hypoxic hypoxia and transition of the matrix metalloproteinases system state from antiproteolytic (due to the prevalence of TIMP-1 over MMP-1) to proteolytic.

The concentration of MMP-1 in amniotic fluid of rabbit fetuses after acute general prenatal hypoxic hypoxia correlated with the weight of the fetus ($r=0.58$, $p<0.001$, $n=35$), which was not observed in the control group ($r=-0.172$, $p=0.324$, $n=35$). At the same time, the correlation of the concentration of MMP-1 in amniotic fluid with the mass of the placenta was revealed neither in the group of pregnant rabbits subjected to acute general hypoxic hypoxia ($r=0.14$, $p=0.425$, $n=35$), nor in the control group ($r=-0.16$, $p=0.358$, $n=35$). Thus, the level of accumulation of MMP-1 in amniotic fluid seems to be determined by the mass of the fetus, not by the mass of the placenta.

It is remarkable to detect the concentration of MMP-1 and TIMP-1 in amniotic fluid of rabbits in acute general prenatal hypoxic hypoxia ($r=0.37$, $p=0.028$, $n=35$), which was not observed in amniotic fluid of rabbits in the control group ($r=0.01$, $p=0.957$, $n=35$). This indicates that the matrix metalloproteinases system was not only activated in acute general prenatal hypoxic hypoxia, but also regulated by limiting the activity of MMP-1 through TIMP-1.

Given the relative brevity of hypoxic effect on the body of the fetus, these results can be interpreted as activation of the matrix metalloproteinases system caused by decompartmentalization of components of the matrix metalloproteinases system with their output into amniotic fluid, rather than activation of gene expression. In view of the fact that the concentration of MMP-1 in amniotic fluid after acute general hypoxic hypoxia was higher than the concentration of TIMP-1, it may be assumed that MMP-1 is a more mobile element of the system than its inhibitor and is released faster into amniotic fluid.

Possible sources of MMP-1 and TIMP-1 can include the fetal lungs, the contents of the intestines and the membranes of the fetus [7]. It appears that longer hypoxic effects through the growing imbalance between the levels of enzymes and their inhibitors of the matrix metalloproteinases system can accelerate the degradation of components of extracellular matrix of the fetus, rupture of the fetal membranes, and delivery.

Conflict of interest. The authors declare no conflict of interest.

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HAEMATOLOGICAL PROFILE IN RATS WITH HYPERCAPNIC HYPOXIA AFTER COURSE ADMINISTRATION OF MEXIDOL

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Research objective. To study the reaction of the hemostasis system to the single effect of hypercapnic hypoxia of maximum intensity in rats and the possibility of correction of hemostasiological disorders with the help of preliminary course use of the antihypoxic drug – mexidol.
Materials and methods. In this study, adult male Wistar rats (48 animals) with the average weight of 274.0±32.0 g were used. Rats were kept on a standard diet, food and water were served once a day between 10 and 11 o'clock. In the evening, animals were subjected to a single hypercapnic hypoxia in a special flow chamber. The state of hypercapnic hypoxia of maximum intensity was modeled at the content of O_2 – 5.0%, CO_2 – 5.0% during a single 20-minute exposure. As a training regime, a 30-fold course of mexidol was used, the drug was administered intraperitoneally in rats at a dose of 50 mg/kg 1.5 h before the hypercapnic hypoxia exposure.
Results. After a single hypercapnic hypoxia exposure of maximum intensity, a shortening of the start clotting time (CT), an increase in the angle α° and the maximum clot firmness (MCF) was recorded. The clot formation time (CFT) decreased as well and the maximum clot lysis (ML) increased. With the single hypercapnic hypoxia exposure of maximum intensity, after the course administration of mexidol, a decrease in the maximum clot firmness (MCF) was recorded.
Conclusions. The single effect of hypercapnic hypoxia of maximum intensity was characterized by a shift of hemostatic potential towards hypercoagulation on the background of fibrinolytic blood system activation. Preceding hypercapnic hypoxia of maximum intensity, the course use of the antihypoxic drug, namely mexidol, significantly reduces the thrombotic risk.
Key words: *hypercapnic hypoxia, hemostasis, thromboelastography, mexidol.*

Acute hypercapnic hypoxia (HH) occurs when the operation of the oxygen supply system is inadequate with the decreased oxygen concentration under hermetic condition, and elevated carbon dioxide concentration. HH is also observed in some cardiovascular, respiratory and blood system disorders [3].

It is established that HH provokes a complex integral reaction in the human body and animals, where a certain role is assigned to the hemostasis system [7]. It was previously found that different HH modes mark a shift in the hemostatic balance towards thrombinemia [4]. At the same time, other studies show that HH causes platelet activation, coagulation elongation [2] and activation of the fibrinolytic blood system [11].

Currently, human survival in acute HH is ensured with individual life support means [12]. However, their use is limited due to the bulkiness, high cost, operation complexity and the ability to restrict movement and vision, as well as to impede the intake of food, water, etc. [3, 5]. At the same time, it is possible to maintain viability in acute hypoxia with the antihypoxic properties of drugs at a sufficiently high level [1].

The energy deficit underlying any hypoxia forms, including HH, leads to qualitatively similar metabolic and structural changes in various organs and tissues: the occurrence of acidosis, activation of free radical oxidation, damage to biological membranes, affecting both the lipid bilayer and membrane proteins. Among the pharmacological drugs of metabolic type of action, a special place is occupied by antihypoxant mexidol [1], which is a succinate-containing derivative of 3-oxypyridine (2-ethyl-6-methyl-3-hydroxypyridine succinate).

Mexidol (ethylmethylhydroxypyridine succinate) inhibits platelet aggregation caused by collagen, thrombin, ADP and arachidonic acid, inhibits phosphodiesterase of cyclic platelet nucleotides, and protects blood cells from mechanical injury [1]. It is found that mexidol inhibits platelet and leukocyte aggregation and adhesion, increases erythrocyte plasticity, and improves blood rheological properties, thereby eliminating normocapnic hypoxia [6].

It is shown that mexidol normalizes both vascular-platelet (which is manifested in the preservation of the platelets and their properties) and coagulation mechanisms, as well as fibrinolytic properties of blood in normocapnic hypoxia from the hemostatic system. This could be the basis for drug therapy in hemostatic disorders caused by exposure to normocapnic hypoxia [11].

It is worth noting that in literature there are no data on the antihypoxants effectiveness in HH modeling.

In connection with the above, the purpose of this work was to study the reaction of the hemostatic system to a single exposure to hypercapnic

hypoxia of maximum intensity in rats and the possibility of correcting hemostatic disorders with the preliminary course of mexidol.

Materials and methods

The studies were performed on 48 mature male Wistar rats of body weight 259.0±36.0 g. All experimental animals were divided into 4 groups: two control groups (n=12x2) and two experimental groups (n=12x2).

The 1st and 2nd experimental groups were subjected to a single HH exposure reaching maximum intensity by placing rats in a chamber with a gas mixture containing 5.0±0.5 % O_2 and 5.0±0.5 % CO_2 for 20 minutes. In addition, the 2nd experimental group of animals daily received intraperitoneal administration of mexidol (50 mg/kg) for 30 days prior to the experimental exposure.

The mode of maximum intensity of hypercapnic hypoxia was selected experimentally, which observed 100% animal survival.

The control groups were placed in the same chamber for a similar time period as the experimental groups; however, in this case, atmospheric air was pumped by the compressor instead of the gas mixture, and a 0.9% NaCl solution was introduced instead of mexidol following the same pattern.

A special flow chamber was used to simulate the HH, where a given mixture of gases was supplied with a compressor at a speed of 15 L/min into it. The chamber had an outlet connected by means of a hose to a container filled with water, which ensured the bleed from the chamber of high-pressure gases. The gas chamber composition was controlled by the O_2+CO_2 gas analyzer Microlux (Microlux OOO, Yekaterinburg, Russia).

Blood sampling in all animals was performed by anesthesia with intraperitoneal administration of 5 mg/100 g zoletil solution.

Blood for the study in a 5 ml volume was obtained by sampling from the hepatic sinus into a polystyrene syringe containing 0.11 M (3.8%) sodium citrate solution (blood-citrate ratio 9:1). Prior to the experiment, during the week of adaptation to vivarium conditions, all rats were kept in standard conditions according to the requirements of Good Laboratory Practice (GLP). Animals were treated according to the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directives 86/609/EEC [8]. Anesthesia and sacrifice procedures were performed according to the rules for conducting animal experiments.

The hemostasis system here was assessed by thromboelastography, an integral method for investigation. Thromboelastometry was performed on the ROTEM Gamma instrument (Pentapharm GmbH, Germany) using the Start-tem reagent.

The thromboelastography decoding considered the following parameters:

Clotting time (CT). It is the time from the beginning of the analysis until the recognizable clot formation start by adding reagents and calcium. The clotting time is an important parameter of coagulation factor activation, as well as its balance with the corresponding inhibitors.

Clot formation time (CFT) CFT displays the kinetics of a persistent clot formation by platelets and fibrin. The clot formation time depends mainly on the number of platelets and especially on their participation in clot formation. In addition, the clot formation time is affected by the fibrinogen level and its polymerization tendency.

Alpha angle (α) – the angle built tangentially to the thromboelastogram from the point of the clotting time. Displays the growth rate of the fibrin network and its structure formation (increase in clot strength).

The maximum clot firmness (MCF) gives information on the maximum amplitude of clot formation reached by the time fibrinolysis is activated. MCF is one of the most important parameters in thromboelastometry.

Maximum lysis (ML) corresponds to the maximum fibrinolysis intensity detected during the analysis and is defined as the lowest amplitude after reaching MCF.

All digital data obtained during the study were subjected to statistical processing. The results of the studies are presented in the form of m [25% ÷ 75%], where m is the median in the sample population, [25% ÷ 75%] – the 25th and 75th percentile. The reliability of the differences was estimated using the nonparametric Mann–Whitney U-test. Differences were considered reliable at a level of statistical significance $p<0.05$. To process and store the obtained experimental material, databases were created using the Microsoft Excel 2010 spreadsheet program. Statistical processing of the results was carried out using mathematical statistics programs Jmp Statistical Discovery v 6.1.2 and Biostat 5.03 on a personal computer.

Results and discussion

A comparative analysis of the results of thromboelastography data recorded after a single exposure to HH of maximum intensity, without/after preliminary administration of mexidol for 30 days is given in the table (Table 1).

According to thromboelastography, after **a single exposure to HH of maximum intensity**, a shortening of the clotting time (CT) by 47.0% ($p<0.001$) was registered against the background of an increase in the α angle by 32.0% ($p<0.01$) and the maximum clot firmness (MCF) by 18.0% ($p<0.001$). Clot formation time (CFT) was also significantly shortened by 42.0% ($p<0.001$). The increase in the fibrinolytic system functional activity was demon-

strated by a twofold increase in the maximum lysis (ML) index ($p<0.05$). Figure 1 and Figure 2 aid visual clarity of the thromboelastograms of animals from the control and experimental groups. In the experiments described above, it was shown that a single exposure to HH of maximum intensity without previous course administration of mexidol is accompanied by activation of both platelet and coagulation units of hemostasis, and the activation of the fibrinolytic system of blood.

Table 1

Indicators of hemostasis system, registered at the end of a single exposure to maximum intensity hypercapnic hypoxia (O_2 – 5 %, CO_2 – 5 %) without/after preliminary 30-day administration of mexidol

Methods of research	HH of maximum intensity without the mexidol introduction (n=10)	HH of maximum intensity at the end of 30-fold mexidol administration (n=10)
CT, s	124.0 [116.2÷140.3]*** (Δ-47 %)	188.7 [179.3÷190.5] (Δ+8 %)
α	78.0 [72.3÷84.0]** (Δ+32 %)	67.2 [64.0÷72.8] (Δ+4 %)
CFT, s	72.0 [67.4÷76.0]*** (Δ-42 %)	94.4 [85.5÷96.6] (Δ+1 %)
MCF, mm	79.0 [70.6÷82.4]*** (Δ+18 %)	68.0 [65.3÷71.0]** (Δ-11 %)
ML, %	2.0 [1.8÷2.3]* (Δ+200 %)	0.0 [0.0÷0.0] (Δ0 %)

*Notes: the data are presented in the form of Me – sample median; [25÷75] – sample percentiles; n – number of observations; Δ – statistically significant finite difference of hemostasis system factors in experimental animals relative to their values in control (per cent); the statistical significance differences with data in the control group indicated as: * – for p<0.05; ** – for p<0.01; *** – for p<0.001; CT – coagulation time; α – the angular constant; MCF – the maximum amplitude of the TEG; CFT – clot formation time; ML – maximum lysis.*

The recorded changes are partially confirmed by the results obtained by W.D. Toff (2006) who showed that inhalation of a hypercapnic mixture (5.0% CO_2 in the air) stimulated hemocoagulation due to increased contact and phospholipid activation of coagulation triggers, increased thromboplastin and thrombin activity, decreased anticoagulant potential and non-enzymatic fibrinolysis [11].

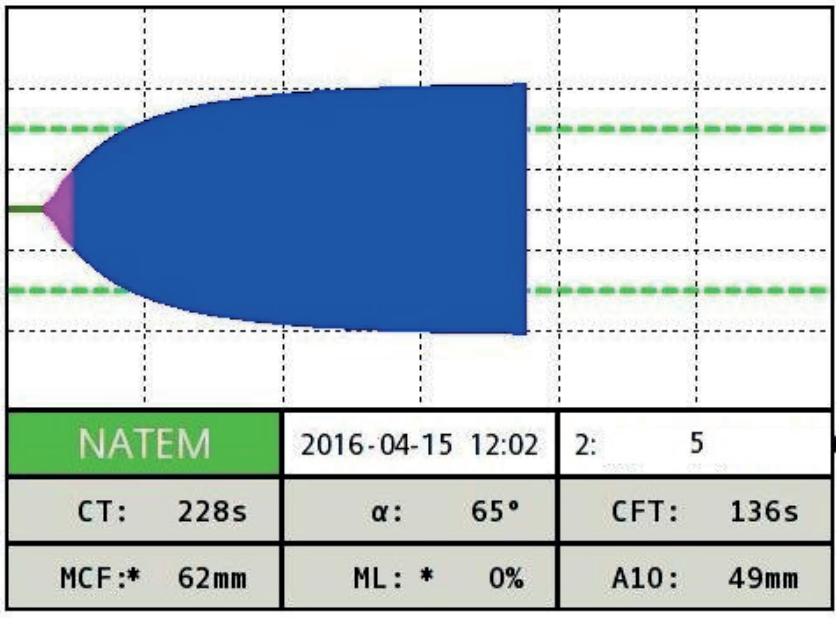

Figure 1. Thromboelastogram (control group, animal No. 5) recorded after a single stay in the chamber for 20 minutes under normal atmospheric pressure.

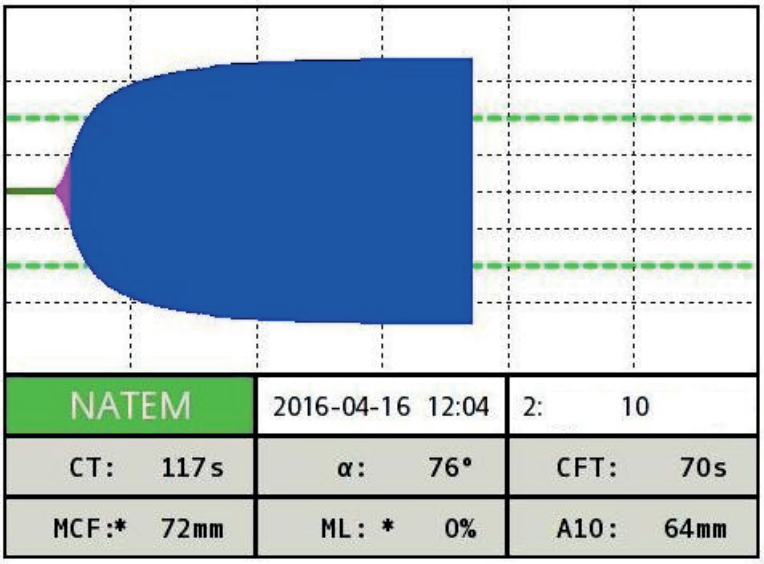

Figure 2. Thromboelastogram (experimental group, animal No.1) recorded immediately after a single exposure to hypercapnic hypoxia of maximum intensity (O_2 – 5%; CO_2 – 5%) for 20 minutes.

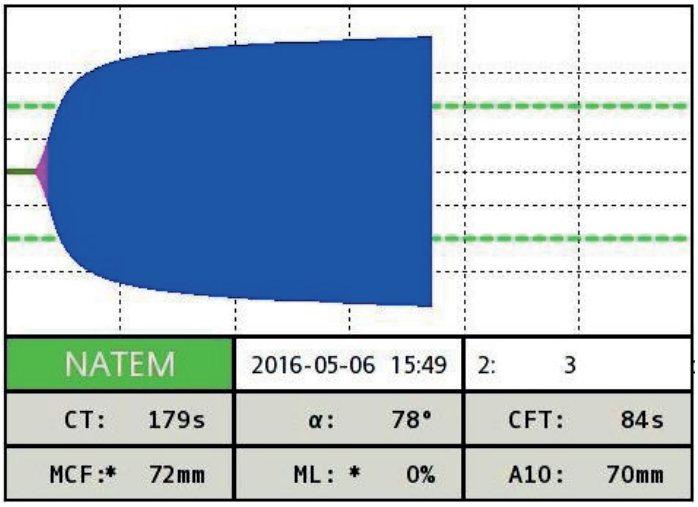

Figure 3. Thromboelastogram (control group, animal No. 3) registered with a single exposure to hypercapnic hypoxia of maximum intensity (O_2 – 5%, CO_2 – 5% – 20 minutes) after 30-fold administration of 0.9% NaCl solution.

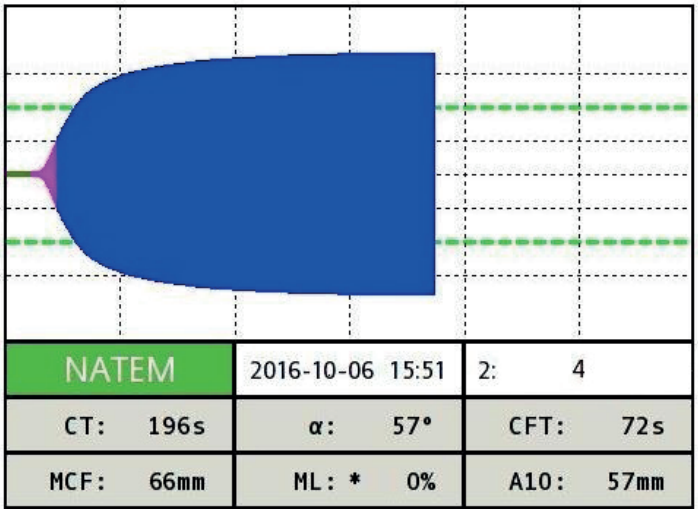

Figure 4. Thromboelastogram (experimental group, animal No. 4) registered with a single exposure to hypercapnic hypoxia of maximum intensity (O_2 – 5%, CO_2 – 5% – 20 minutes) after 30-fold mexidol administration.

According to thromboelastography, a shortening of the maximum clot firmness (MCF) by 11% ($p<0.01$) was registered with a single exposure to HH of maximum intensity after the course administration of mexidol, there were no significant differences in other indicators. Thromboelastograms obtained in animals from the control and experimental groups are given as an example (Figure 3 and Figure 4). The preliminary course administration of mexidol largely normalized the hemostatic picture recorded after a single exposure to HH of maximum intensity. At the same time, there was found only a decrease in the MCF, which may be associated with a decrease in the number of platelets, as well as inhibition of their ability to aggregate. It may be explained by the fact that CO_2 can stimulate endothelial NO synthase [9], which leads to a NO concentration increase in the bloodstream, which has powerful antiaggregation and disaggregation effects [10]. In addition, mexidol is known to independently improve blood circulation in the vascular bed, inhibiting platelet aggregation and increasing the antithrombogenic potential of the blood.

Conflict of interest. The authors declare no conflict of interest.

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CONTROLLABLE AND SOCIALLY SIGNIFICANT INFECTIOUS DISEASES: PROBLEMS AND SOLUTIONS

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Yu.V. Lobzin

The article reflects topical issues of infectious pathology, among which preventive vaccination is of special importance. The role of preventive vaccination was noted not only in reducing morbidity and mortality from infections, but also in preventing oncologic and somatic diseases, limiting the antibiotic resistance growth. Reasons for insufficient vaccination coverage of the population were revealed, measures for their elimination were proposed. Experience of children scientific and clinical center of infectious diseases and domestic experience of preventive vaccination effectiveness were presented. The program of preventive vaccination in St. Petersburg aimed at implementing the strategy "St. Petersburg – a city free of infections" was described.
Key words: *preventive vaccination, infections, program, problems, solution.*

The problem of infectious diseases is highly relevant today. Against the background of the close attention paid in recent years to this issue in the Russian Federation, some progress has been achieved: it was possible to stabilize the incidence of HIV infection and tuberculosis, Russia received a certificate from the World Health Organization (WHO) as a country where the spread of rubella was stopped [1-5].

At the same time, a number of unresolved issues define the continuing significant role and relevance of infectious diseases at the present time. First of all, this is the problem that is directly related to the biosafety of the population. Infectious diseases, along with infectious complications in surgery and other medical specialties, determine up to 35% of fatal cases [1]. Therefore, one of the most important tasks facing health care in the coming years should be not only to increase life expectancy but also to reduce the frequency of fatal cases of infections.

The increasing number of reports on the important role of infectious agents in the development of somatic diseases deserves special attention: pathology of the heart, lungs, central nervous system. Thus, the Children's Scientific and Clinical Center of Infectious Diseases demonstrated that children during the influenza epidemic die not only from pneumonia but also from damage to the heart and central nervous system by influenza viruses [6].

The number of officially registered cases of infectious diseases in the country is about one million a year, which is up to 30-40% of all diseases. In children, this figure is much higher than in adults and is up to 90%.

Infections are also of key importance in the solution of demographic problems. In the structure of mortality from infectious and parasitic diseases of the adult population, HIV infection takes more than 50%, tuberculosis – 32%, viral hepatitis, sepsis, meningococcal infection – more than 5%. At the same time, in children, the first in the structure of deaths are community-acquired pneumonia (up to 35%) and meningococcal infection (up to 25%) [1-5].

The economic burden of infectious diseases is enormous. According to the State report of 2018, the cost of treatment of respiratory tract infections amounted to 513 bln rubles, tuberculosis – to 35 bln rubles. Overall, the total costs amount to at least a trillion rubles. Unfortunately, the costs of treating infections that can be prevented by vaccination are significant. Even without taking into account losses from rotavirus, pneumococcal, hemophilic infections and infectious diseases caused by papillomaviruses, they amount to at least 16 bln rubles [3].

In the history of humankind, people have developed three main directions in controlling infectious diseases which include epidemiological measures, hygiene, treatment with the use of antibacterial and antiviral medication, and vaccinal prevention. And each of these measures has its limitations.

Epidemiology and sanitary are crucial. Preventive measures limit the spread of infection through quarantine measures, but they cannot eradicate the infection. Smallpox (variola) was the only infection to be eradicated. In this case, the infectious agent is kept in laboratories that with the cancellation of smallpox vaccination and with virus entering the environment can lead to the development of an epidemic.

Treatment of infectious diseases also does not significantly affect the spread of infections. For a number of infections, such as polio and measles, the effectiveness of treatment is limited. The treatment of bacterial infections is also fraught with enormous difficulties. The decrease in the effectiveness of antibacterial drugs and the growth of antibiotic resistance constitute a threat in the 21st century. This complicates the solution of problems associated with limiting the spread of infectious diseases through treatment.

Vaccination is of key importance in the control of infectious diseases. With the start of vaccination, the Soviet Union experienced a dramatic decline in the incidence of: measles by 500 times, diphtheria by 200 times, mumps by 150 times, pertussis (whooping cough) by 40 times, tetanus by 50 times. There was a decrease in the incidence of hepatitis B in the first years of vaccination by more than 4 times. Attempts to revise these approaches in the 90s led to tragic consequences. For example, only in St. Petersburg, the abolition of vaccination against diphtheria led to 300 deaths among children. Since 2000, vaccination against viral hepatitis B and tuberculosis have become mandatory in maternity hospitals, which has led to a decrease in the incidence of acute hepatitis by 50 times and tuberculosis by 5 times. Moreover, according to WHO experts, due to the introduction of vaccination, life expectancy has increased by 30 years. An example of the effectiveness of vaccination is a decrease in the incidence of influenza against the background of an annual increase in vaccination coverage. Thus, in 2019, almost 50% of the population was vaccinated, leading to the absence of serious epidemically significant cases and a reduction in deaths [6-8].

Vaccination today is the eradication of infectious agents; it is the disease monitoring, reduction of complications, deaths, infant mortality; it is the economic benefit, the conditions for health and mobility; it is the condition for full working capacity, population effect, social equality, since vaccination is subject to all the people, regardless their financial situation; it is the prevention of somatic and oncological diseases; it is also a new aspect because the international community considers vaccination as a leading means of combating antibiotic resistance.

In our country, implementation of vaccination is based on the Federal Law FZ-157 «On immunoprophylaxis of infectious diseases». According to the law, the Federal budget currently provides vaccination against 12 infections such as hepatitis B, tuberculosis, pneumococcal infection, Hemophilus infection, polio, pertussis (whooping cough), diphtheria, tetanus, measles, mumps, rubella, and influenza. Many countries have already expanded their immunization programs to 15-17 (some countries – to 19) nosological entities. Moreover, the expediency of broadening the spectrum of the vaccinated population is obvious. Thus, the idea of mandatory pneumococcal vaccination of older people, closely associated epidemiologically with children, is actively being worked out. It is essential to expand the vaccination against hemophilic infection type B for all categories of children, not just risk groups.

In his decree dated 29 May 2017, the President of the Russian Federation declared «the Decade of childhood». Prevention of infections, which remain the leading cause of child deaths and disability, is a priority in the implementation of this program. Up to 50% of all child deaths are currently associated with some form of infection. Moreover, up to 35% out of 670 thousand children with disabilities acquired disability due to infectious diseases. In this regard, supplementary immunization programs should be considered as a possible solution to this problem. This additional immunization is a real possibility to improve infection control. With the active involvement of staff members of the Children's Research and Clinical Center for Infectious Diseases in St. Petersburg, a vaccine prevention program, aimed at reducing incidence, disability, and mortality, was developed. The key in this program is the strategic direction: «St. Petersburg is a city free of infections».

This program can be taken as a basis and applied in any region and city. This can be the basis for expanding the vaccination program of the population of certain territories by improving regional immunization programs. The program describes the mechanisms for integrating additional vaccinations into the National Immunization Schedule, for example, pertussis (whooping cough) with an incidence higher than the average in Russia, Haemophilus influenzae type b, not at only risk groups. For many years, St. Petersburg has been implementing supplementary immunization programs, with annual funding for supplementary vaccination of children in closed institutions against varicella, hepatitis A, and Haemophilus influenzae type b.

The features of the vaccination in various infectious diseases are identified as pressing issues. Pertussis is an example of such diseases. A number of specialists describe it as an «unmanageable infection». The incidence of this infection doubled in Russia in 2018, and whooping cough ranked second in the growth rate of the incidence, after measles. At the same time, the combined vaccines with a pertussis component registered in Russia allow for vaccination in all age groups. Maximum and timely coverage of preventive vaccinations is necessary. The best tactic is the vaccination of children in the first two years of life, who are most often sick, with mandatory revaccination of children. Immunity lasts no more than seven years. This leads to the fact that the child, vaccinated in the first year of life, at the time of starting school does not have a protective antibody titer causing a second peak incidence of whooping cough. At the same time, parents are also ill, and their diagnosis is complicated by the common changing nature of the disease pattern.

The incidence of whooping cough in St. Petersburg is higher than in the Russian Federation, the highest is in children under one year, and school-age children prevail in the pattern of cases. One possible solution is the widespread use of combined vaccines for vaccinations of children of the first five years and the introduction of revaccination of children 6-7 years of age. The introduction of these measures is not very expensive, but it will

save children from severe complications of whooping cough. The results of mathematical modeling show that the economic efficiency of vaccination of one cohort can be more than 2.6 million rubles.

The other infection is Haemophilus influenzae. The experience of St. Petersburg shows that due to the widespread introduction of combined vaccines in children of the first year of life, the incidence of H. influenzae decreased by 4 times. H. influenzae is one of the leading causes of severe pneumonia, sepsis and meningitis, with mortality up to 10% and a high risk of complications (deafness from 2 to 10%, 70% of patients need rehabilitation). Treatment of five patients with Haemophilus meningitis in 2016 in the intensive care unit of the Children's Scientific and Clinical Center of Infectious Diseases, excluding the cost of further therapy and rehabilitation, exceeds 2 million rubles. The use of combined vaccines for revaccination of a cohort of children at 18 months could solve the problem of protection against Haemophilus influenzae in children 1.5 years and older. In calculating the pharmacoeconomic model, conducted by the specialists of the Children's Scientific and Clinical Center of Infectious Diseases, and using a 5-component combined vaccine, the savings for one child will amount to almost a thousand rubles.

Another formidable infection is *a meningococcal infection.* Nowadays one out of five who gets meningococcal disease will die from the infection. And the death of more than half occurs within the first day of the disease. This is the only infection with peracute fulminant course of the disease. This is largely determined by the frequent development of a severe complication – Waterhouse–Friderichsen syndrome (WFS), characterized by bleeding into the adrenal glands, as well as the development of septic shock. At the same time, the incidence of meningococcal infection has increased by 15% over the past year. Those patients who can be saved with severe forms of meningococcal infection need rehabilitation.

In recent years, 43 million rubles have been spent on the treatment of only 23 patients from severe forms of meningococcal infection in the intensive care unit of the Children's Scientific and Clinical Center of Infectious Diseases. If a tetravalent combined vaccine was used with wide coverage for children of the first year in St. Petersburg, this would lead to a six-fold decrease in the incidence rate and a direct economic benefit of up to 14 million rubles [11]. It is also worth noting that recently there has been the emergence of new strains of meningococci, in particular, meningococcal serogroup W135, which has not been detected before. This strain was transformed as a result of gene transfer of the meningococcal C serogroup in 2010-2011 during mass gatherings during the Hajj. This strain causes extremely severe forms of the disease, with a 29% mortality rate, and acquires features of antibiotic resistance to a number of medications.

The fact of the varicella epidemic in the Russian Federation should not be hidden but recognized, and all efforts should be directed to reducing the incidence of both children and adults. The severity of varicella is based not on skin lesions, but on frequent complications from the nervous system, and primarily in the form of encephalitis. Herpesviruses are characterized by necrosis, in other words, viruses kill cells, leading to severe complications and consequences in the distant future. In addition, mention should also be made of another property of these viruses – their lifelong persistence in the human body, which is associated with their role in the violation of the functioning of the immune system, which leads to the development of somatic pathology, for example, atherosclerosis of blood vessels. According to recent data, the nervous system damages caused by varicella among hospitalized children are observed in 43% of cases. At the same time, the example of the Kachkanar municipality (Kachkanar is a town in Sverdlovsk Oblast, Russia), where total vaccination against varicella was carried out, indicates the possibility of reducing the incidence of this infection to almost zero.

Rotavirus infection as a pediatric problem. Up to 70% of all intestinal infections in the modern structure of incidence are viral gastroenteritis. The first place among them is followed by rotavirus, and then norovirus infections, viral gastroenteritis of other etiology are less common. In the Russian Federation, the incidence of rotavirus infection is 83.26 per 100,000 population. Rotaviruses are associated with up to 27% of all outbreaks of acute intestinal infections. In St. Petersburg, the incidence of rotavirus infection is more than 100 per 100,000 population, and the cost of treatment of one case of rotavirus gastroenteritis is almost 24,000 rubles. In 2018, there were 8 fatal cases of rotavirus infection among children.

In many countries of the world, all children aged under 12 months are vaccinated against rotavirus infection. The incidence of rotavirus infection in vaccinated patients in those countries that introduced mass vaccination decreased by 70-90% in the next year and by 15-70% in those age groups that were not subject to vaccination. Also, the incidence of hospitalizations of children decreased by 30-50% and mortality from intestinal infections by 20-40%. Russia experienced the same in Krasnoyarsk Krai, where after the introduction of rotavirus vaccination, the decrease in the frequency of hospitalization was 30% within a year after vaccination. This indicates that vaccination against rotavirus infection is effective and should be introduced into the Federal Immunization Schedule.

Pneumococcal infection is one of the most common among both children and adults. The widespread introduction of vaccination against pneumococcal in-

fection in the Russian Federation has significantly reduced the incidence of this infection. Despite the high costs of providing wide coverage for pneumococcal vaccination (about 4 billion rubles), the ratio of vaccination costs to the amount of prevented economic damage is 1:3. Pneumococcal vaccination in adults with chronic diseases showed high efficiency, as indicated by the example of Krasnoyarsk Krai. Thus, pneumococcal vaccination is an effective tool in the prevention of the disease.

Human Papillomavirus infection as a social problem is undeniable. Cervical cancer, laryngeal papillomatosis, anogenital warts make the surface of an iceberg of those severe oncological diseases that are caused by papillomaviruses. In 62 countries, HPV vaccination is introduced into the National Immunization Schedule. In Australia, where total HPV vaccination has been introduced for all girls and boys aged 11-13 years, the progress in combating the virus is so great that the incidence of HPV infection is practically reduced to zero. This problem has not yet been solved in St. Petersburg. Every year there are no less than 500 new cases of cervical cancer, 40 cases of vulva and vagina cancer, and 2.5 thousand new cases of anogenital warts. In terms of incidence, St. Petersburg is ahead of other cities of the Russian Federation by two or three times. This phenomenon is explained by the geographical location of the city and its tourist attraction, which creates prerequisites for sexually transmitted infections. Since 2010, the World Health Organization recommends that all countries add HPV vaccination to their program. Such recommendations have been already implemented in almost 100 countries. In our country, the issue with the introduction of HPV vaccination also requires a solution to protect the young generation from this severe infection unpleasant in its complications, it is especially relevant since the fight against cancer is a priority not only in the world but also in Russia. The cost of the vaccine is an obstacle to implementation in our country. However, even taking into account the high economic costs, a wide (at least 30%) coverage of the cohort is associated with an economic benefit of hundreds of millions of rubles [12].

In general, the economic analysis of the further expansion of vaccination, with regard to the situation in 2019, is possible savings of 1722.1 million rubles.

Still, a large number of outstanding problems remain. The Russian Federation remains below the standards of the WHO-recommended Immunization Schedule: there is no mandatory Haemophilus influenzae vaccination in all children, from rotavirus and papillomavirus infections, and varicella. There are no differentiated schedules for children and adolescents, adults, persons of different groups of social, professional, medical risk for infectious diseases, travellers and migrants.

Separately, it is worth considering the rapid alarming growth of the anti-vaccination movement, which, unfortunately, involves medical professionals. To date, there is no unified training of doctors on vaccine prevention in universities. It is necessary to develop social, state propaganda of vaccination. In a number of countries, including Finland and France, where vaccination is mandatory for the entire population, tough measures are legislated to combat the anti-vaccine lobby.

Thus, infections retain their social and economic importance. The widespread development of immunization of the population will help to reduce healthcare costs, protect people with concomitant diseases, especially older age groups, reduce incidence and mortality. The implementation of the decrees of the President of the Russian Federation on reducing mortality and increasing life expectancy cannot be achieved without expanding the vaccination program. Vaccination is effective if the following principles are met: its life-long implementation; wide coverage of the population; selective approach to priorities of an epidemic situation and depending on regional characteristics. It is very important that the regions and their governors are legally entitled to have additional programs and Immunization Schedules, only their social position and awareness of the importance of vaccination are needed. Only one meningococcal infection can be an example, where the treatment of its severe forms requires a stay in the intensive care unit of a specialized hospital, long-term hospitalization, high-tech procedures such as microfiltration, removal of toxins and cytokines from the blood, close, constant care and economic costs up to 25 million rubles per patient, which is not yet possible to implement nationwide. Vaccination is the most effective and economically viable method to prevent infections, which requires further implementation since it is also aimed at solving the problem of antibiotic resistance and at a reasonable distribution of medical resources.

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EFFECTIVENESS OF THE PREVENTIVE CONSULTING IN OUTPATIENT AND INPATIENT PHASES: RESULTS OF THE REALIZATION IN THE ORGANISED COMMUNITY

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Implementation of corporate programs of primary prevention of cardiovascular diseases (CVD) is a promising direction for preservation of the health of the working population.
Research objective. To assess the effectiveness of the CVD prevention program, including the provision of preventive care at the hospital stage in an organized workforce.
Materials and methods. The study included drivers and assistant drivers of the locomotive depot of the Barnaul station. Individual preventive consulting was conducted in a polyclinic, rehabilitation (fitness and health) center, in-patient hospital. The monitoring study was carried out in representative samples, in 2010, the sample was 224 men, in 2016 – 123 people. The evaluation of behavioral, cardiometabolic, psychosocial risk factors, temporary disability (TD) was carried out.
Results. Preventive consulting involving outpatient and inpatient staff led to a reduction in smoking prevalence by 40.3%, hypodynamia by 18.2%, excessive alcohol consumption by 52.3%, insufficient consumption of vegetables and fruits by 29.6%, hypercholesterinemia by 15.7%, abdominal obesity by 11.2%, and resting tachycardia by 12.7%. The multidisciplinary approach with the involvement of a psychologist allowed to achieve the correction of psychosocial factors: there were no cases of subclinical and clinical anxiety and depression, a high level of psychosocial stress was detected in one person. There was a decrease in the CVD incidence with TD by 1.8 times, in arterial hypertension by 1.3 times.
Conclusion. The results confirm the effectiveness and necessity of implementing preventive programs in the labor community by incorporating measures to establish them into the national health strategies, health sector reforms, and plans to improve the effectiveness of health systems.
Key words: *workforce, employees of locomotive crews, cardiovascular diseases, prevention, risk factors*

Cardiovascular diseases (CVD) are remaining to be the major cause of death globally, they are annually responsible for 17.3 million deaths [1] – 31.5% of all world's population deaths and 45% of all deaths from noncommunicable diseases (NCD), which include four types of diseases: cardiovascular, oncological, respiratory diseases and diabetes mellitus (DM). This justifies the necessity of implementation of comprehensive measures, among which primary prophylaxis of the CVDs – first of all, early identification and management of risk factors – is a high-priority and feasible measure to improve the population situation in Russia and to enhance the personnel and labor capacity [2].

Data of the domestic and foreign studies using various programs of the preventive consulting indicate their high effectiveness regarding a number of important indicators for cardiovascular prophylaxis [3]. Prophylaxis is effective: compliance with the principles of healthy lifestyle and reduction of the level of the main risk factors within the population can prevent up to 80% of premature deaths from CVDs [4]. Thus, comprehensive programs of prophylaxis, multidisciplinary approach in the management of the behavioral risk factors, involvement of nurses, dietitians, psychologists, etc. are the most effective measures. To help to change one's lifestyle, approved cognitive-behavioral methodologies (i.e. a motivational interviewing) are recommended. With a high risk of CVDs, integrated interventions, combining medical resources with a training of healthy lifestyle, physical exercises, stress management, consultation on psychosocial risk factors are implemented [5, 6].

A lifestyle determining the establishment of person's health generally depends on the pattern of behavior and life mindsets, which are formed and encouraged by the social environment. The impact of professional factors is of great importance, these factors, on the one hand, may obstruct the maintaining healthy lifestyle and, on the other hand, may be among significant risk factors of the development of CVDs. A profession of a railroad engineer makes greater demands on the psychophysical state of an organism [7], it has been proved that CVDs are the leading diseases among this category of workers, and this reduces the effectiveness of transportations and increases the risk of technological disasters [8]. In this regard, it seems urgent to improve the coverage and quality of work of occupational health services with an increase in their preventive orientation, as previous experience shows that the implementation of preventive programs in work

communities is effective and economically feasible [9, 10, 11].

The purpose of the study was to assess the effectiveness of the program of prevention of CVDs, including the providing of preventive care in hospital phase in the organized work community.

Materials and methods

The presented study is a part of the comprehensive activities on development and introduction of the organizational model of common prophylactic environment in the organized work community of the locomotive depot of Barnaul railway station. This model ensures continuity of prophylactic measures in the workplace, in the pre–trip medical examination station, in the hospital, in the rehabilitation (health and fitness) center, in the inpatient department and encourages a long-term management of risk factors and preventing CVD development among locomotive crew workers. Population strategy is focused on informing employees about risk factors and on motivating them towards healthy lifestyle with the help of mass media – a section *Let's protect our professional longevity* in the newspaper *Altai Locomotive Engineer,* where articles on healthy lifestyle are published regularly. Information displays with commercials promoting healthy lifestyle and emergency mutual and self–aid skills under life-threatening conditions are located in the halls of the hospitals, inpatient department, rehabilitation (health and fitness) center, pre-trip medical examination station. In the Russian Railways, corporate sports events aimed at the promotion of an increase in physical activity take place. In addition, in order to eliminate hypodynamia of employees, there is a gym in the health and fitness (rehabilitation) center located on the territory of the locomotive depot. Another important activity of the population strategy might be the School of Health in the workplace, which is held in the locomotive depot of Barnaul station and showed its effectiveness in the management of risk factors [12].

The high-risk strategy, focused on the earliest possible identification of individuals with high total cardiovascular risk (CVR) and implementation of active preventive measures with the purpose of full management of risk factors, is being put into practice in several directions. Since 2010, in addition to the School of Health in the workplace, the in-depth individual preventive consultation has been carried out in the rehabilitation (health and fitness) center for locomotive crews and in the Policlinic of JSC Russian Railways. During the individual preventive consultation, an assessment of behavioral, cardiometabolic and psychosocial risk factors, an assessment of the risk category of the development of cardiovascular complications, a joint phased lifestyle improvement plan are being made.

In 2013, a prophylaxis office in the inpatient department of the Divisional Clinical Hospital at Barnaul station was opened in order to ensure continuity and full coverage of employees with preventive measures. A group preventive consultation is conducted daily in the prophylaxis office (Health Schools on managing main risk factors and teaching skills of emergency mutual and self-aid in the development of cardiovascular complications). In addition, all hospitalized workers of locomotive crews undergo in-depth individual preventive consultation. A specialist in medical prevention works in cooperation with a psychologist and a dietitian. This measure was introduced in connection with the importance of initiating an adequate preventive intervention before discharge from the hospital, since preventive treatment after discharge tends to decrease rather that increase, the number of patients receiving adequate therapy decreases over time without reaching the target levels of risk factors [6].

This study assessed the effectiveness of preventive consultation conducted in the policlinic, rehabilitation center and inpatient department for the period from 2010 to 2016. A monitoring study was carried out within representative selections of locomotive crew workers. In 2010, the selection was 224 people (average age of 42±5.6 years), in 2016 – 123 people (average age of 43.9±7.2 years). Inclusion criteria: male gender; age of 20–55 years; an occupation of train engineer or assistant engineer; consent to participate in the study. Exclusion criteria: symptomatic arterial hypertension (AH); deterioration of AH; AH of the III stage and 3rd degree; ischemic heart disease (IHD) and other associated clinical conditions; DM; chronic diseases with insufficiency of organs and systems; acute illnesses; refusal to participate in the study.

Assessment of CVD risk factors was carried out in accordance with the Guidelines on Cardiovascular Prevention, 2017 [5].

1. Smoking. Smokers were considered individuals who smoked ≥1 cigarette per day.

2. The consumption of alcohol. Excessive alcohol consumption – ≥2 standard doses per day for men. The preferred alcoholic beverage was also evaluated.

3. Dietary medical history, frequency and number of servings of vegetables and fruits (excluding potatoes). Insufficient consumption of vegetables and fruits was stated at less than 5 servings per day.

4. Adequate physical activity: moderate physical activity of 150 minutes per week, intense aerobic physical activity of 75 minutes per week, the equivalent combination of moderate and intense physical activity, daily walking of 3 km or more.

5. Excess body weight and obesity, including abdominal obesity (AO). The evaluation of height and weight, the calculation of body mass index (BMI) was conducted: normal body weight is at BMI of 18.5–24.9; overweight – 25.0–29.9; I degree obesity – 30.0–34.9; II degree obesity – 35.0–39.9;

III degree obesity – ≥40. Waist circumference (WC) was measured in a standing position, in the middle between the lower edge of the chest and the ilium crest in the mid–axillary line (not the maximum size and not at the navel). At WC ≥94 cm for men, AO was confirmed.

The identification of chronic psycho-emotional stress was carried out using the Reeder L.G. questionnaire. [13]: 1–2 points – high; 2.01–3.0 points – average; 3.01–4.0 points – low level of psychosocial stress.

Screening of anxiety and depression was carried out using the HADS Hospital Anxiety and Depression Scale. When interpreting the data, the total indicator for each subscale was considered: 0–7 points – the norm; 8–10 points – subclinically expressed anxiety/depression; 11 points and above – clinically expressed anxiety/depression.

Laboratory studies included fasting of total cholesterol (TC) test. Hypercholesterolemia (HC) was established at values of TC >5 mmol/l or in accordance with the cardiovascular risk.

Diagnosis of AH was carried out during routine medical examinations, as well as according to the results of monitoring blood pressure (BP), measuring BP at the pre-trip medical examination or self-monitoring of BP. All employees with AH were under clinical supervision with the prescription of antihypertensive therapy [8]. At the time of the study, all men included in the selections in 2010 and 2016 reached the target level of BP.

Indicators of the office heart rate (HR) were evaluated during a general clinical examination. Heart rate at rest for more than 80 bpm was considered.

The analysis of the incidence with temporary disability (TD) for CVD at large and for AH (the number of cases per 100 employees) was conducted.

Data processing. Statistical methods for processing research results: methods of medical statistics, applications package STATISTICA 10.0. Before statistical processing, selection power and size were assessed, and the distribution was checked for normality using the Kolmogorov-Smirnov, Lilliefors and Shapiro-Wilk tests. To compare the average values, the paired Student's t-test was used with a distribution close to normal; at a distribution distinct to normal, the Wilcoxon W-test was used. A pairwise comparison of frequencies was carried out using the Pearson $\chi 2$ criterion. The parameters presented in the results of the study have the following notations: M – arithmetic mean value; SD – standard deviation; n – the absolute number of individuals in the group; % – proportion of individuals of their total number in the group; p – achieved level of statistical significance. A value of $p<0.05$ was taken for a critical level of statistical significance.

Results and discussion

Depending on the duration of communication with the medical worker, preventive interventions are divided into three degrees of low, medium and high intensity (no more than 30, 31–360 and more than 360 minutes, respectively) [14]. There is evidence that more intense or longer targeted interventions give more expressed and lasting results in relation to both behavioral changes and patient prognosis [3, 15]. Moreover, a combination of knowledge and skills of various medical workers (doctors, nurses, psychologists, psychotherapists, dietitians, rehabilitation therapists, sport medicine specialists) allow implementing multimodal behavioral interventions that help optimize prevention options (class I, level of evidence A) [6]. In a much smaller number of cases, prophylactic interventions are aimed at one of the risk factors, i.e. nutritional interventions or interventions aimed at increasing risk factors, management of hyperlipidemia, etc. [16, 17].

According to systematic reviews and meta-analyses, in addition to the behavioral aspects of lifestyle, several individual impacts associated with work, including working stress, long working hours and shift work, were associated with cardiovascular morbidity and mortality [17, 18]. Therefore, the active introduction of preventive programs in the work communities in arduous labor is an important interdisciplinary task of healthcare. In our study, a set of preventive measures covering the workplace, clinic, hospital is carried out with the involvement of psychophysiologists, a psychologist, a dietitian, which led to the improvement of the train engineers' lifestyle and successful management of behavioral risk factors.

Over the period from 2010 to 2016, there was a positive trend of reducing the smoking rate among employees of locomotive crews (Table 1): 72.8% smoked in 2010, 32.5% – in 2016, that is by 40.3% less ($\chi^2=53.0$; $p<0.001$).

The next analyzed behavioral risk factor is alcohol consumption. It appeared that in 2010 the consumption of alcoholic beverages of more acceptable values per day was more common than in 2016 by 52.3% ($\chi^2=88.5$; $p<0.001$). An examination of train engineers and their assistants in 2016 revealed that 12.2% did not drink alcohol, while in 2010 there were no such men at all. Of alcoholic beverages in 2010, men preferred to drink beer in 70.1% of cases, after ten years – in 18.7% of cases, which is by 51.4% less ($\chi^2=84.0$; $p<0.001$).

According to the results of our study, a positive effect was obtained on the management of the level of physical inactivity: in 2010, the value of men with an insufficient level of physical activity was 75.9%, in 2016 – 57.7%, which is less by 18.2% ($\chi^2=12.4$; $p<0.001$), predominantly due to daily walking more than 3 km.

Table 1

Dynamics of CVD risk factors of locomotive crew workers when conducting preventive consultation

CVD risk factors	2010 (n=224)		2016 (n=123)	
	abs.	%	abs.	%
Smoking	163	72.8	40	32.5*
Excessive alcohol consumption	137	61.2	11	8.9*
No consumption of alcohol in the past year	-	-	15	12.2
Beer preference	157	70.1	23	18.7*
Insufficient consumption of vegetables and fruits	132	88.0	57	46.3*
Low physical activity	170	75.9	71	57.7*
Excess body weight and obesity (BMI ≥25 kg/m²)	175	78.1	83	67.5***
Abdominal obesity (WC >94 см)	178	79.5	84	68.3***
Hypercholesterolemia (TC >5 mmol/l)	130	58.0	52	42.3**

*Note: *p<0.001; **p<0.01; ***p<0.05 – statistical significance of differences in indicators in 2010 and 2016.*

The data are consistent with a number of other studies in which managing preventive measures in organized communities were focused on improving behavioral risk factors [19, 20].

Recent studies have shown that consumption of fresh and dried fruits/vegetables of 500–600 g per day is associated with a decrease in total mortality by 42% [21]. In our study, this risk factor had the following dynamics: 75.9% of men had inadequate consumption of fruits and vegetables in 2010, while preventive measures were taken after six years, this risk factor had 46.3%, which is less by 29.6% ($\chi^2 = 30.7$; $p < 0.001$).

Lifestyle improvement, management of behavioral habits during preventive measures in the work community of locomotive crew workers led to positive results in reducing the frequency of cardiometabolic risk factors (Table 1). An analysis of anthropometric indicators revealed that overweight and obesity (BMI ≥25 kg / m²) were observed in 78.1% of employees in 2010, in 2016 – in 67.5% of the examined employees, i.e. a decrease in this risk factor by 10.6% was noted (χ^2=4.7; p<0.05). The frequency of AO over six years decreased by 11.2% (χ^2=5.4; p<0.05): 79.5% and 68.3%, respectively, in 2010 and 2016. In 2010, an increase in the level of cholesterol over the target values in the studied group was 58.0%, in 2016 the number of men with this risk factor was less by 15.7% (χ^2=7.9; p<0.01) and amounted to 42.3%.

In recent years, the prevalence of arterial hypertension among people of working age in Russia has grown and is currently 43%, and this was due to an increase in the prevalence of high blood pressure among the male population (47.8%) [5, 22]. In the studied community of locomotive crew workers, the AH frequency in 2010 amounted to 42.0%, in 2016 it slightly decreased (by 5.4%) to 36.6% (without statistical validity). All men received antihypertensive therapy and reached the target level of blood pressure. The average office blood pressure did not differ between years (Table 2): in 2010 – 125.5±8.5/78.4±7.6 mm Hg, in 2016 – 125.4±8.0/78.1±7.3 mm Hg.

The average office heart rate in 2010 was 77.1±7.2 bpm and exceeded the average office heart rate in 2016 (75.1±6.8 bpm) by 2 bpm (p<0.05). When analyzing HR of more than 80 bpm, it emerged that after six years, men with resting tachycardia appeared by 12.7% less often (χ^2=7.1; p<0.01): 28.1% and 15.4%, respectively, in 2010 and 2016 (Table 2).

Table 2

Dynamics of hemodynamic parameters in locomotive crew workers during preventive consultation

CVD risk factors	2010 (n=224)	2016 (n=123)
Average office BP, mm Hg (M±SD)	125.5±8,5	125.4±8.0
Office diastolic BP, mm Hg. (M±SD)	78.4±7.6	78.1±7.3
AH (abs., %)	94 (42.0)	47 (36.6)
Office HR, bpm (M±SD)	77.1±7.2	75.1±6.8**
HR >80 bpm (abs., %)	63 (28.1)	19 (15.4)*

*Note: *p<0.01; **p<0.05 – statistical significance of differences in indicators in 2010 and 2016.*

Various prophylactic screening programs and recommendations for preventing consultation of the adult population have been developed and are widely used in different countries of the world [23, 24]. For more than 25 years in the United States there is a non-governmental organization – the United States Preventive Services Task Force (USPSTF) [14]. Experts of this panel recommend for residents over 18 years of age with overweight and obesity, as well as with additional CVD risk factors (increased blood pressure, hyperlipidemia, impaired glucose tolerance or metabolic syndrome) intensive (more than 360 min) preventive consultation on healthy nutrition and physical activity for prevention CVD. In addition, it is recommended for adults over 18 years of age without obesity and other risk factors also be referred to preventive consultation, i.e. healthy people with low CVR. Available data indicate the advisability of conducting preventive consultation for CVD risk factors in this population, although the magnitude of the positive effect is small [25]. However, the risk of CVD and its complications is closely related to working factors. Obviously, fundamentally different factors play a significant role in the pathogenesis of CVD in locomotive crew workers, primarily factors related to working conditions: workplace stress, social burnout, shift work during night hours, noise load, etc. [26, 27]. Therefore, in the community of locomotive crew workers we are studying, preventive measures are carried out for all men, including the categories of low and moderate CVR. The relevance of the full coverage of preventive technologies for the entire community, regardless of the category of CVR, is confirmed by recently obtained data by E. Zhidkova and co-authors. A retrospective analysis of 119 cases of sudden death of locomotive crew workers in the period from 2009 to 2017 was carried out. In most cases, a combination of risk factors in the development of CVD was detected, but the risk of cardiovascular death on the SCORE scale was moderate [28].

A long-term exposure and the performance of official duties by railway transport specialists in challenging conditions of a professional environment is the reason for the functioning of an individual on the verge of a person's psychophysiological capabilities. An analysis of studies in the field of occupational health and longevity of railway transport specialists shows that the assessment and management of psychosocial factors play an important role in the prevention of cardiovascular complications in this category [7].

According to the results of the assessment of psychosocial factors among locomotive crew workers in our study, a high level of psychosocial stress (self-assessment according to the Reeder scale) in 2010 was found in 16.1%, average – in 44.2%, low – in 39.7% of men (Table 3). Significant differences were obtained after 6 years, in 2016, most men had a low level of stress – 93.5%, which is more by 53.8% (χ^2=94.7, p<0.001). An average stress level was found in 5.7%, which is less by 38.5% (χ^2=55.5, p<0.001), a high level of stress was found in 1 person (0.8%) (χ^2=19.4, p<0.001).

Table 3

Dynamics of psychosocial factors in locomotive crew workers during preventive measures

Psychosocial factors	2010 (n=224)		2016 (n=123)	
	abs.	%	abs.	%
Reeder Psychosocial Stress Self-Assessment				
high	36	16.1	1	0.8*
average	99	44.2	7	5.7*
low	89	39.7	115	93.5*
HADS Hospital Scale, A (Anxiety) and D (Depression)				
Norm A	170	75.9	123	100
Subclinical A	46	20.5	0	0
Clinical A	8	3.6	0	0
Norm D	196	87.5	123	100
Subclinical D	28	12.5	0	0
Clinical D	0	0	0	0

*Note: *p<0.001 – statistical significance of differences in indicators in 2010 and 2016.*

In 2010, 75.9% and 87.5% of men had the normal values on the HADS Anxiety and Depression scale, respectively, 20.5% had subclinical anxiety, 12.5% had subclinical depression, and 3.6% had clinical anxiety. When analyzing these indicators after 10

years, it was found that all examined people had low indicators on the anxiety and depression scale.

For the period (2010–2016), the incidence rate with temporary disability (number of cases per 100 employees) was analyzed: for CVD, it decreased by 1.8 times (from 6.7 to 3.9), by 1.3 times – for arterial hypertension (from 4.0 to 3.1).

Conclusions

1. Conducting preventive consultation with outpatient and inpatient care in the work community led to a decrease in the frequency of smoking by 40.3%, physical inactivity by 18.2%, excessive alcohol consumption by 52.3%, insufficient consumption of fruits and vegetables by 29.6%, hypercholesterolemia by 15.7%, abdominal obesity by 11.2%, resting tachycardia by 12.7%.

2. The use of a multidisciplinary approach involving a psychologist made it possible to achieve the management of psychosocial factors: no cases of subclinical and clinical anxiety and depression were indicated; a high level of psychosocial stress was detected in one person.

3. There was a 1.8-fold decrease in the incidence rate with temporary disability for CVD, a 1.3-fold – for arterial hypertension.

The results confirm the effectiveness and necessity of implementing preventive programs in work communities by including measures for creating such programs in national health strategies, health sector reforms and plans to improve the effectiveness of health systems.

Conflict of interest. The authors declare no conflict of interest.

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FEATURES OF THE CLINICAL COURSE OF IBD IN CHILDREN OF BARNAUL ACCORDING TO THE RESULTS OF WORK OF THE CITY GASTROENTEROLOGICAL DEPARTMENT

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The research objective was to conduct a comparative study of the clinical course of ulcerative colitis and Crohn's disease in children. The study was conducted on the basis of the hospital register of patients with ulcerative colitis and Crohn's disease in the gastroenterological department of the Children's City Hospital No. 1 of Barnaul for the last ten years. The study included 15 children, among them, 6 with UC, 6 with CD, and 3 with nonspecific colitis. The analysis of the clinical picture, the results of biochemical and endoscopic examinations was carried out. It was established that there are features of the clinical course characteristic for each disease. Inflammatory changes in UD and CD are weak or moderate, especially in the case of CD. Of the inflammatory markers, the increase in the calprotectin level is of the greatest importance in the diagnosis of IBD. Among patients with UC, distal forms (proctitis, proctosigmoiditis) were more often found in 66,6% of children, patients with CD more often showed the form with lesion of the large and small intestine – 66.6%. The results of colonoscopy and histological studies do not allow to differentiate UC and Crohn's disease without taking into account all clinical and laboratory data.
Key words: *ulcerative colitis, Crohn's disease, children.*

Inflammatory bowel diseases, which include Crohn's disease and nonspecific ulcerative colitis, are the most severe pathologies of the gastrointestinal tract and are characterized by chronic, steadily progressive course with the risk of developing intestinal and extraintestinal complications.

P.V. Glavnov et al. give the following statistics of the prevalence of IBD in Russia: prevalence in Moscow Oblast: 22.3 cases per 100 000 population, annual increase of patients – 5–20 cases per 100 000 population. High prevalence rates were also observed in Europe (ulcerative colitis – 505 per 100 000 in Norway; Crohn's disease – 322 per 100 000 in Germany) and North America (ulcerative colitis – 286 per 100 000 in the USA; Crohn's disease – 319 per 100 000 in Canada) [1]. According to E.A. Kornienko, the incidence of ulcerative colitis in children during the last five years has increased by 2 times, and the incidence of Crohn's disease in children population in Saint Petersburg was already ahead of UC by 2.3 times by 2013 [2].

Inflammatory bowel diseases have a clear tendency to "rejuvenate" among the population. According to a number of foreign and domestic studies, previously the peak of incidence fell at the age of 20–30 years, the second peak of 55–60 years, but by now, there are quite a lot of cases known of infant, early and youthful forms of disease. Crohn's disease and ulcerative colitis are difficult to diagnose, as they are very similar in the clinical picture, laboratory indicators, macro- and microscopic data [3].

N.A. Malakhinova showed that in patients with Crohn's disease the predominant symptoms were abdominal pain (87%), rapid stool (64.7%), diarrhea (55.3%), body weight loss (52.3%), increased body temperature (55.3%). In patients with ulcerative colitis, the most frequent symptoms were blood admixture in the stool (87.1%), rapid stool (80.2%), abdominal pain noted in 73.3% of cases. Weight loss, increased temperature, fistulas, strictures, and anal fissures were significantly more common in Crohn's disease [4]. Similar data were received by E.S. Bodryagina et al. According to these authors, the most frequent manifestations in ulcerative colitis and Crohn's disease were diarrhea (70%), abdominal pain (68%), rectal bleeding (47%), fever (47%), with diarrhea and rectal bleeding being more common in patients with ulcerative colitis (82% and 61% respectively), and abdominal pain – in patients with Crohn's disease (79%) [5].

L.V. Bubnova drew the similar conclusions, emphasizing that ulcerative colitis differs in the presence of blood in the stool in 92% compared to 5% of children with CD, with symptoms of intoxication (fever, weight loss, asthenic syndrome) more pronounced in CD [6].

Thus, both diseases have common clinical features and, despite some differences, differential diagnosis is difficult. In terms of laboratory data, ulcerative colitis and Crohn's disease are characterized by inflammatory changes in general and biochemical blood tests. E.A. Kornienko gives the results of studies showing the greater severity of inflammatory changes in patients with Crohn's disease in comparison with ulcerative colitis [2].

Colonoscopy is an important diagnostic procedure for differentiating the IBD, but it does not guarantee the correct diagnosis.

V.G. Rumyantsev (2015) emphasizes that in difficult diagnosis cases it is necessary to use a set of histological, macroscopic, endoscopic and radio-

logical features, as well as data of the history of the disease and clinical picture [7].

Thus, the study of the prevalence, peculiarities of clinical course, endoscopic and microscopic signs of inflammatory bowel diseases remains an urgent task.

The aim of the study was to conduct the comparative characterization of the course of ulcerative colitis and Crohn's disease in children of Barnaul on the basis of the analysis of the hospital register of the gastroenterological department of the Children's City Hospital No. 1 of Barnaul for the last 10 years.

Materials and methods

To solve this problem, standardized questionnaires for each patient were developed and filled out on the basis of medical records. According to the hospital register of the gastroenterological department of the Children's City Hospital No. 1 of Barnaul, 15 children were registered with the diagnosis of IBD for the last 10 years. Among them, there were 6 children with Crohn's disease, 6 with ulcerative colitis, and 3 with indeterminate colitis. Subsequently, 12 children diagnosed with Crohn's disease or ulcerative colitis were included in the study.

Results and discussion

Among patients with UC, girls and boys distributed equally: 3 girls (50%) and 3 boys (50%). The mean age of the debut was 11.6±1.6 years (minimum – 10 years, maximum – 14 years). In the evaluation of clinical symptoms in descending order, it was found that diarrhea was observed in 6 (100%) children, blood admixture in the stool in 5 out of 6 children (83.3%), more often a small amount of blood in each portion. In all children, diarrhea was weakly or moderately pronounced to 3–5 episodes of liquid stool per day and only in 1 child up to 10–12 times a day. Pain syndrome was noted much less frequently: in 2 (33.3%) children, the pain had "IBS-like character": it increased before and decreased after defecation. Of the "symptoms of anxiety", only 1 (16%) child had moderate weight loss. Thus, UC more often showed with manifestations of "hemorrhagic colitis", weakly or moderately expressed.

The analysis of laboratory data revealed that inflammatory markers were observed in a few children. Acceleration of ESR was observed in 1 case, as well as moderate leukocytosis and the increased fibrinogen level. More often, there was an increase in the level of CRP – in 3 (50%) children, in 2 cases the increase was insignificant (from 1.5 to 3 norms) and in 1 case more than 20 norms. Anemia was noted in only 2 (33.3%) patients. It should be emphasized that even in the presence of clinical signs of hemorrhagic colitis, hidden blood in the stool was detected in only 2 (33.3%) children. A more significant inflammatory marker was an increase in the calprotectin level detected in 5 (83.3%) children, the average level was 1435±774.5 μg/g.

According to colonoscopy, all children (100%) had erosive ulcerative changes: in 2 children on the background of inflamed mucosa, ulcerative changes prevailed, and in 4 – erosive ones. When assessing the prevalence of the process, the most frequent changes were proctitis and proctosigmoiditis – in 4 (66.6%) children, 1 child (16.6%) was diagnosed with left-sided colitis and 1 (16.5%) – total colitis.

Histological data were nonspecific, in 50% of children, the histological picture corresponded to chronic colitis of varying degrees of severity and in 50% – chronic colitis with mucous erosion.

In the group of patients with CD, there were 2 girls (33.3%) and 4 boys (67.7%). The mean age of the debut was slightly lower than in UD and amounted to 9.6±3.1 years (minimum – 5 years, maximum – 14 years). Compared to UC, the clinical course of CD was dominated by "extraintestinal manifestations" in some patients. Among the intestinal symptoms, abdominal pain of varying intensity was more frequent: in 4 (66.6%) patients, localized more often in hypogastrium. In 1 child in the debut of the disease, there was extremely intense pain in the right iliac region, which required laparoscopy. Diarrhea was detected in 3 (50%) children, but diarrhea was more pronounced than in UC, 5 to 16 times a day. Blood admixture in the stool was observed only in 2 (33.3%) children. Among the "extraintestinal" manifestations, there was a physical developmental delay in 2 children (33.3%) and weight loss in 3 children (50.0%), long-term fever in 1 (16.6%), hypoproteinemic edema – in 1 (16.6%) child. In general, in only 2 (33.3%) children the disease debuted from the "hemorrhagic colitis" clinic, in 1 (16.6%) child from the severe pain syndrome in the right iliac region combined with physical developmental delay, in 1 (16.6%) child from the hypoproteinemic edema combined with physical developmental delay, and in 2 (33.3%) children from the significant weight loss combined with weak intestinal symptoms.

Inflammatory changes in patients with CD were more pronounced than in the group of children with UC. An increase in ESR, as well as an increase in the level of CRP, was observed in 4 (66.6%) patients, fibrinogen in 2 (33.3%). Of the inflammatory markers, an increase in the level of calprotectin was also very significant, it was revealed in all patients examined (100%). The average level was 2160±190.9 μg/g. The presence of hidden blood in the stool, as well as anemia, was observed more often than in the case of UC – in 4 (66.6%) children.

In the evaluation of endoscopic manifestations, according to the data of colonoscopy, in 6 (100%) patients, erosive ulcerative changes of the intestinal mucosa were determined, as in the case of UC. Ulcerative changes were observed slightly more of-

ten than in UC – in 4 (66.6%) patients, and erosive ones – in 2 (32.4%).

The histological picture was nonspecific as in the UC and corresponded to chronic colitis or ileitis of varying degrees of severity, in some children – with the formation of erosions. By the prevalence of the process, children more often revealed the form with lesions of the large intestine and small intestine – 4 (66.6%), 1 (16.6%) child – the form with lesion of the large intestine and 1 (16.6%) – with lesion of the small intestine.

In our study among patients with IBD, patients with UD and CD were found with equal frequency. This corresponds to the data on the increase in the incidence of CD in recent years; according to E.A. Kornienko, for the period of 2013, the incidence of Crohn's disease of child population in Saint Petersburg was already ahead of UC by 2.3 times [2].

In terms of gender differences, in our study, there were 7 boys (58.3%) and 5 girls (41.7%) among patients with IBD. In the NUC group, the number of boys and girls was equal (3/3), while boys (4/2) marginally dominated in the CD group. The timing of the manifestation of both diseases was similar, however, the debut of CD, according to our data, falls on an earlier age. This does not contradict most of the previously mentioned works. So, according to E.A. Kornienko, CD is marginally more common in boys in childhood. M.F. Denisova also showed that CD is most often found among boys. However, unlike our data, according to the results of this study, the peak incidence of CD fell on adolescence (12–18 years), and UC was diagnosed in children a little earlier: from 7 to 18 years [8].

As for clinical features of the course of IBD in children, the majority of authors agree that in the clinic of UC in children the phenomenon of hemorrhagic colitis prevails, and CD can manifest various symptoms, including extraintestinal. We have already given information from the works of N.A. Malakhinova, E.S. Bodryagina, E.I. Kornienko to confirm this fact [4, 5]. According to our data, manifestations of hemorrhagic colitis were also more typical for UC; pain syndrome and various extraintestinal manifestations such as physical developmental delay, fever, hypoproteinemic edema were characteristic of CD.

Colonoscopy is a very important diagnostic procedure for differentiating IBD. However, endoscopic data are not always enough to differentiate Crohn's disease and ulcerative colitis. In our study, the changes revealed according to the data of colonoscopy and histological study were nonspecific in CD and UC. The most frequent signs were chronic inflammatory process and erosive ulcerative defects of the mucosa. The localization and length of the process were more important for diagnostics compared to the nature of changes. In our study, distal forms (proctitis and proctosigmoiditis) dominated by the prevalence of the process in patients with UC, less often subtotal and total forms of lesions. This is mildly contrary to the data of other studies. So, N.G. Bandaevskaya found that in patients under 11 years total large intestine lesion occurs in 93% of cases, there are practically no patients with left-sided colitis in this age group and distal one is observed in 7%, but among adolescents over 15 years there is a higher frequency of segmental forms [9]. Other authors received similar data. Perhaps, these differences are due to the fact that our patients were dominated by teenagers.

As for CD, among our patients, there were children with lesions of the large intestine and small intestine, less often there was the form with isolated lesion of the large intestine or with lesion of the small intestine. Such data were given by N.A. Malakhinova, according to which the following localizations of the disease were determined in patients with CD: ileocolitis – 44.7%, ileitis – 22.3%, colitis – 20%, upper gastrointestinal lesion – 10.5% [4]. Moreover, according to N.G. Bandaevskaya, the most often revealed form was the one with ileocecal lesion (70%), large intestine lesion (30%), lesion of anorectal area (20%), upper gastrointestinal lesion (5–15%) [9].

Thus, the study of the peculiarities of the clinical course of IBD in children remains an urgent task. The acquisition of new data will improve the quality of diagnosis and treatment.

Conclusions

1. Among patients with IBD, patients with ulcerative colitis and Crohn's disease were revealed with equal frequency, no significant gender differences were found. The mean age of the debut of the disease in both groups did not differ significantly: UC – 11.6±1.6 years (minimum – 10 years, maximum – 14 years); CD – 9.62±3.06 years (minimum – 5 years, maximum – 14 years). In the clinic of UC, patients with hemorrhagic colitis symptoms prevailed compared to CD, where hemorrhagic colitis phenomena were observed in 33.3% of children, and in 67.7% the disease debuted with intense pain syndrome or with various extraintestinal manifestations.

2. Inflammatory changes in UD and CD are weak or moderate. Of the inflammatory markers, the increase in the calprotectin level is of the greatest importance in the diagnosis of IBD. Laboratory differences between UC and CD consisted in a more pronounced inflammatory response in the case of CD.

3. Among patients with UC in our study, distal forms prevailed – 66.6% of children, 1 child (16.6%) was diagnosed with left-sided colitis and 1 (16.5%) – with total colitis. Patients with CD more often revealed the form with lesions of the large intestine and small intestine – 66.6%, 16.6% – the form with lesion of the large intestine and 16.6% with lesion of the small intestine. The results of

colonoscopy and histological studies do not allow to differentiate UC and Crohn's disease without taking into account all clinical and laboratory data.

Conflict of interest. The authors declare no conflict of interest.

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