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RETROSPECTIVE EVALUATION OF THE EPIDEMIOLOGICAL SITUATION OF ACUTE INTESTINAL INFECTIONS OF BACTERIAL AND VIRAL ETIOLOGY IN THE PREFLOOD PERIOD

Altai State Medical University, Barnaul

G.G. Onishchenko, I.P. Saldan, C.I. Tribunsky, V.B. Kolyado, Ye.V. Kolyado

The article presents the results of a retrospective epidemiological analysis of the incidence of acute intestinal infections in prefreshet period in Altai Krai and the Republic of Altai. As a result of the analysis topical epidemiological precursors deteriorating situation in both territories before the seasonal floods were established, and the peculiarities of the morbidity of individual nosological forms in the territories of Russia with a high risk of flood development were investigated.

Key words: floods, flood situation, infectious morbidity.

The state of human environment becomes especially important during the period of extreme hydrometeorological events. The analysis of literature sources revealed, that along with the economic damage caused to the society, they could lead to the development of serious medical consequences. The destruction of life support systems created an unfavorable sanitary-hygienic environment in large territories (there are formed new factors of epidemiological risk and the existing ones are activated). In that context, the emergency situations of biological and social nature quite often take place [1, 4, 5, 7, 8, 13]. According to other authors, flood destroy the infrastructure of inhabited areas, threatened the life of population, which requires the evacuation of victims to more safe regions and the creation of temporary accommodation facilities for them. The indicated factors aggravate the epidemiological situation and predetermine mass infectious diseases, primarily, intestinal infections transmitted by water and food. In the structure of acute intestinal infections increases the role of noro- and rotaviral infections [2, 3, 6, 9, 10, 11, 12]. The effect of water on biocoenosis of natural focuses preconditions the realization of sanitary-epidemiological for the population situated in the flood zone, which are realized by the increase of morbidity of such dangerous infectious diseases, as cholera, acute viral intestinal and other infections, moreover, over the last decades, there has been indicated a number of new viruses – causative agents of dangerous infections.

Objective: retrospective epidemiological analysis of morbidity of acute intestinal infections among the population of Altai Krai and the Altai Republic in the preflood period.

Materials and methods

The retrospective analysis of morbidity of population of Alta Krai and the Altai Republic was performed on the basis of the statistical tools “The

information about infectious and parasitical diseases” (form No. 1) for the period of 2004-2013. The statistical data processing was conducted be means of common methods of analysis: calculation of intensive and extensive indexes, creation and processing of time series, mean values (\bar{X}), diversity of their characteristics (σ) and coverage errors (m), calculation of regression coefficients ($R_{x/y}$), approximation. To state the degree of determinacy of variation of criterion variable by predictors, there was implemented the method of regression analysis with construction of trend lines. As a result of regression analysis, there were obtained regression equations with calculated values of regression coefficients. The significance of obtained regressional dependences expressed by mathematical equation was selected on the basis of the approximation coefficient $R^2 > 0,5$. The coefficients of determination show, that the most preferable is the polynominal trend, and the least preferable – the linear one. Graphical support and data processed were performed on a personal computer Intel Pentium by means of standard license programs («SPSS Statistics 20», Excel) in Windows 7 operating environment.

Results and discussion

In Altai Krai in the period from 2010 to 2014 the total volume of infectious diseases is dominated by acute upper respiratory infections, which constitute 93,0%, the second position is occupied by airborne infections – 4,5%, the third position is occupied by acute intestinal infections – 1,5%, the fourth position – by zoonotic and natural focal diseases – 0,1%. The dynamics of acute intestinal infections morbidity among the population of Altai Krai in the period from 2004 to 2013 is characterized by annual increase of the index from $377,1^{0/0000}$ to $397,8^{0/0000}$ by the average annual rate of growth ($R_{gr.}$) $0,6\%$, the long-term average annual index ($X_{p \pm m}$) constituted $390,2 \pm 4,0^{0/0000}$. The trend had a statistically significant character, $R^2 > 0,5$. The AII

(acute intestinal infections) morbidity of unknown etiology also grew from 245,3⁰/₀₀₀₀ to 279⁰/₀₀₀₀ (R_{gr} 1,4%, $R^2 > 0,5$, $X_{p \pm m} = 273,7 \pm 3,3$ ⁰/₀₀₀₀), the AII of determined etiology – from c 89,7⁰/₀₀₀₀ to 116,6⁰/₀₀₀₀ (R_{gr} 3,0%, $R^2 > 0,5$, $X_{p \pm m} = 114,3 \pm 2,2$ ⁰/₀₀₀₀) (Figure 1).

The epidemiological situation of dysentery in Altai Krai for the studied period can be characterized as favorable, the index of bacterial dysentery morbidity decreased from 42,08⁰/₀₀₀₀ in 2004 to 2,2⁰/₀₀₀₀ in 2013 by average annual rate of decrease (R_{de}) 28,0% ($R^2 > 0,5$), the long-term average annual index constituted $2,2 \pm 0,3$ ⁰/₀₀₀₀. The salmonellosis morbidity reduced from 37,6⁰/₀₀₀₀ to 37,2⁰/₀₀₀₀ (R_{de} 3,0%, $R^2 > 0,5$, $X_{p \pm m} = 36,5 \pm 1,2$ ⁰/₀₀₀₀), which indicates the effectiveness of measures to control the stated group of infections conducted in the ter-

ritorial entity of the RF. There had been registered the cases of typhoid fever incidence: 1 case in 2006 and 1 case in 2009. The dynamics of enterovirus infections morbidity (further – EVI) has a multi-directional character: the morbidity of viral hepatitis A infection, noroviruses (for the period from 2010 to 2013) and other AII has an upward (negative) trend. The morbidity of ACI caused by enteropathogenic coliform bacteria (further – EPCB) has a downward (positive) trend. The evaluation of the epidemiological situation of enterovirus infections morbidity in Altai Krai in the period from 2004 to 2013 shows, that the rotavirus morbidity in the territorial entity has a trend to growth from 8,20⁰/₀₀₀₀ to 53,50⁰/₀₀₀₀ (R_{gr} 5,9%, $R^2 > 0,5$, $X_{p \pm m} = 258,1 \pm 11,2$ ⁰/₀₀₀₀).

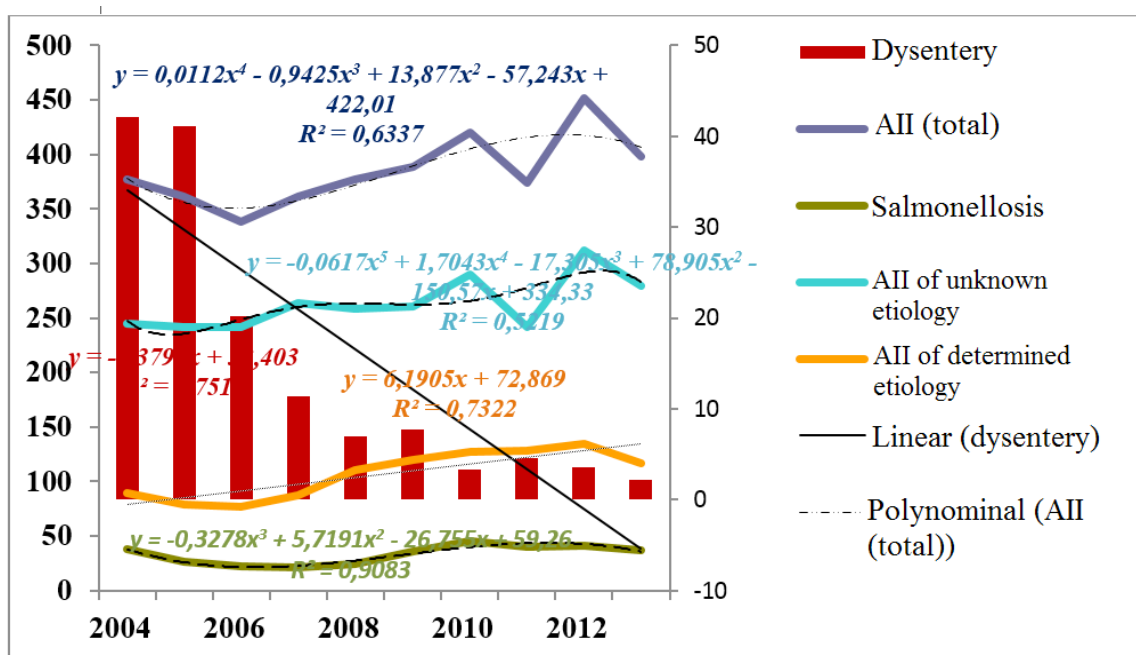


Figure 1. Dynamics of morbidity of AII of bacterial etiology in 2004 – 2013 in Altai krai (per 100 thous. population). (The diagram is built on the basis of Rospotrebnadzor administration of Altai Krai)

It should be noted, that the rotavirus infection is characterized by high relative share (24,0%) in the structure of AII of determined etiology, possesses expressed seasonality during the winter-spring period, high contagiousity, low infective dose, high activity of water and community transmission, resistance in external environment and forms virus carriage. In this regard, it is necessary to monitor the circulation of rotaviruses in the environment, particularly, in the main water, to conduct the rotavirus antigen examination of persons with clinical manifestations of diarrhea. The intensity of EPCB AII morbidity reduction among the population annually constituted 4,5%, which allowed to stabilize the annual average index at the level of $7,5 \pm 0,6$ ⁰/₀₀₀₀. The level of morbidity of other AII increased from 89,7⁰/₀₀₀₀

in 2004 to 116,6⁰/₀₀₀₀ in 2013 (R_{gr} 3,0%, $R^2 > 0,5$, $X_{p \pm m} = 109,1 \pm 2,1$ ⁰/₀₀₀₀). The highest levels of morbidity were registered in 2011 ($P=127,8$ ⁰/₀₀₀₀) and in 2011 ($P=135,1$ ⁰/₀₀₀₀). In the long-term dynamics of viral hepatitis A there is determined the annual average rate of growth 0,5% ($R^2 > 0,5$), the average index for the studied period constituted $4,2 \pm 0,4$ ⁰/₀₀₀₀. In this regard, there can be differentiated 2 period in the long-term dynamics of viral hepatitis A epidemic process. Thus, from 2004 to 2009 the dynamics of viral hepatitis A morbidity was characterized by annual reduction of the index from 6,0⁰/₀₀₀₀ to 1,6⁰/₀₀₀₀ (R_{de} 23,3%), since 2010 the morbidity acquired an upward trend from 3,5⁰/₀₀₀₀ to 6,3⁰/₀₀₀₀ (R_{gr} 21,4%).

For the whole studied period in 2010 there were firstly registered 5 cases of norovirus infec-

tion, while the morbidity of AII caused by noroviruses grew from $0,2^{0/}_{0000}$ in 2010 to $2,1^{0/}_{0000}$ in 2013 ($R^2>0,5$). In the period of 2011-2013 in Altai Krai there were registered 9 hotbeds of group (5 and more cases) diseases, caused by noroviruses, with the total number of diseased – 97, including 77 children. In the structure of infectious morbidity of the Altai Republic AII constitute 4,0% occupying the 3rd position after acute upper respiratory infections (91,1%) and chickenpox (5,0%). The dynamics of AII morbidity among the whole population of the Altai Republic for the period from 2004 to 2013 is characterized by annual growth of the index from $430,8^{0/}_{0000}$ to $540,5^{0/}_{0000}$, by average annual rate of growth 2,6% ($R^2>0,5$), the average long-term index constituted $607,3 \pm 17,2^{0/}_{0000}$. The leading position in the long-term dynamics is taken by acute intestinal infections of unknown etiology (further – AIIUE), the morbidity of which increased from $230,5^{0/}_{0000}$ to $285,2^{0/}_{0000}$ ($R_{gr.}$ 2,4%, $R^2>0,5$, $X_p \pm m = 266,7 \pm 11,4$). The analysis of annual AIIUE morbidity indicates year-round registration of diseases without expressed seasonality.

In the age structure of AIIUE diseased population the share of child population constituted from 57,0% to 65,0%. It should be mentioned, that sporadic cases of morbidity in organized child groups do not have further proliferation and, as a rule, are not connected with the child presence in the child-care institution. In 2007 there was registered the outbreak of AIIUE in the Altai republic, which had a food nature, 27 people suffered, the diagnoses was bacteriologically confirmed – in all patients there was detected *S. enteritidis*. The results of the retrospective epidemiological analysis showed, that the long-term dynamics of AII of determined morbidity among the population of the Altai Republic for 10-year period was characterized by the trend to growth from $128,1^{0/}_{0000}$ to $215,0^{0/}_{0000}$, with the average annual rate of growth 5,9% ($R^2>0,5$). The average long-term morbidity level constituted $258,1 \pm 11,2^{0/}_{0000}$. The salmonellosis morbidity grew from $24,7^{0/}_{0000}$ to $27,5^{0/}_{0000}$ ($R_{de.}$ 1,2%, $R^2>0,5$, $X_p \pm m = 26,4 \pm 3,6$). At the same time, the index of bacterial dysentery morbidity decreased from $46,9^{0/}_{0000}$ in 2004 to $12,8^{0/}_{0000}$ in 2013 by average annual rate of decrease 13,4% ($R^2>0,5$), the average long-term index constituted $55,4 \pm 5,2^{0/}_{0000}$.

In 2013 the index of salmonellosis morbidity constituted $27,5^{0/}_{0000}$, there were registered 58 cases. In 2013 the share of children at the age under 17 constituted 51,7%. The outbreak salmonellosis morbidity was not registered. In the structure of infectious morbidity of the Altai Republic for the period of 2004-2013 AIIUE holds the 1st position, there share is 44,0%. The 2nd position is occupied by AII of determined etiology, 43,0%. The 3rd position is occupied by dysentery constituting 9,0% and the 4th position – by salmonellosis constituting 4,0%. In the Altai Republic along with bacterial

intestinal infections are widespread acute intestinal infections of virus etiology. The carried analysis showed, that for the period from 2004 to 2013 the average long-term rotavirus morbidity index constituted $137,1 \pm 8,2^{0/}_{0000}$, viral hepatitis A (VHA) – $3,0 \pm 1,2^{0/}_{0000}$, other determined AII – $524,7 \pm 16,0^{0/}_{0000}$. In the structure of AII of determined etiology a considerable share is occupied by rotavirus diseases, the morbidity of which has a clear trend to growth. In 2004 there were registered 31 cases of rotavirus infection, the index of morbidity constituted $15,3^{0/}_{0000}$, in 2013 there were registered 254 cases and the index grew up to $120,5^{0/}_{0000}$, by average annual rate of growth 25,7% ($R^2>0,5$) (Figure 2).

In the period from 2011 ($179,4^{0/}_{0000}$) to 2013 ($120,5^{0/}_{0000}$) the morbidity of gastroenteritis of rotavirus etiology decreased by 32,8%. The reduction of infection was registered among all age groups of child population. The disease was primarily registered among the children under 6, who in 2013 constituted 89,3% (in 2012 – 87,0%, in 2011 – 88,9%). Out of total number of diseased the relative share of children under 17 in 2013 constituted 93,3% (in 2012 – 91,2%, in 2011 – 87,0%). In 2013 there were continued the studies of external environment objects (central water supply, decentralized water supply) for the presence of rotavirus antigen. No positive results were obtained. Considering a quite high rate of morbidity of rotavirus infection, there is conducted annual examination of food unit workers for intestinal infections, including viral (rota- and noroviruses). Thus, in 2012, there were examined 480 people, in 2013 – 520 people. In case of positive results there were provided corresponding treatment. VHA morbidity on the territory of the Altai Republic has a sporadic character, there are registered single cases in the city of Gorno-Altaysk and separate districts (Maiminsky, Ust-Kansky).

The morbidity index reduced from $13,9^{0/}_{0000}$ in 2004 to $3,3^{0/}_{0000}$ in 2013 by annual average rate of decrease 14,7% ($R^2>0,5$). In 2013 VHA morbidity among the population under 17 constituted $14,3^{0/}_{0000}$, including the age group of 15-17 years – $51,8^{0/}_{0000}$, among the population over 18 – $2,6^{0/}_{0000}$. In the territorial entity there are provided timely antiepidemic measures in case of morbidity. One of the aims of VHA prevention is the conduction of preventive vaccination, especially for exposed persons in the hotbeds, and also for children and decreed workers. In the period from 2008 to 2013 in terms of “Preventive vaccination” sub-program realization 3113 people were vaccinated against VHA. To monitor the material of laboratory tests of patients with VHA and objects of external environment by means of modern molecular diagnostics methods there was established cooperation with Federal Budget Institution of Science “Central Research Institute of Epidemiology”. In order to monitor the circulation of intestinal

viruses in 2013 there were studied 102 samples of surface waters and 182 samples of main water for the presence of antigen of rotaviruses, noroviruses, the results were negative. During the study

period the morbidity of other AII of determined etiology grew from 358,6‰ to 500,2‰ by average annual rate of growth 3,8% ($R^2 > 0,5$), the average annual index constituted $524,7 \pm 16,0$ ‰.

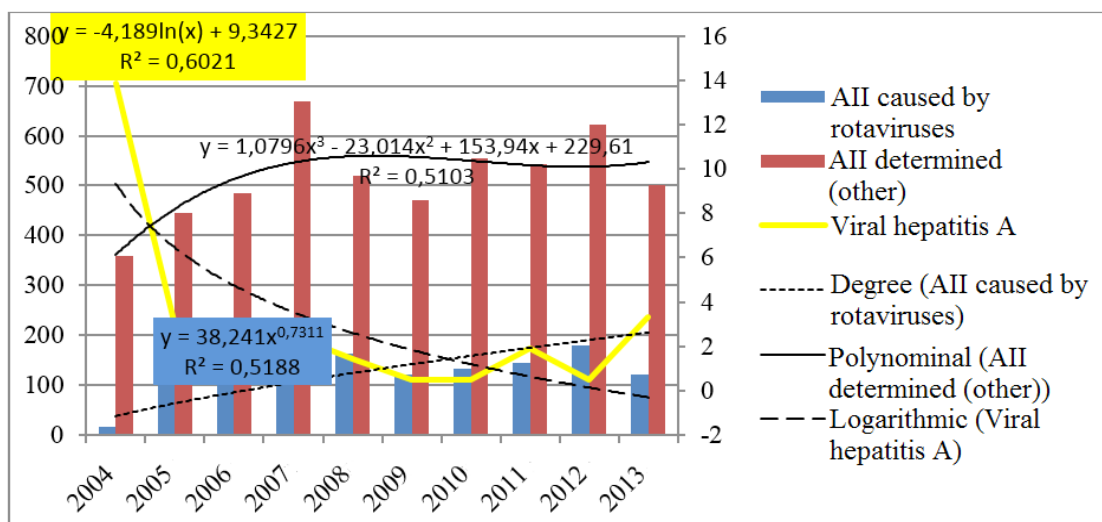


Figure 2.

Dynamics of morbidity of AII of virus etiology (VHA, rotavirus, determined AII, etc.) for the period of 2004-2013 in the Altai Republic (per 100 thous. population). (The diagram is built on the basis of Rospotrebnadzor administration of Altai Krai)

Conclusion

As a result of the conducted retrospective epidemiological analysis there was determined the level, structure and dynamics of infectious morbidity in the pre-flood period in the territories of Altai Krai and the Altai Republic, providing the solution of problems of epidemiological diagnostics in order to substantiate advanced planning of epidemiological measures. The methods of epidemiological analysis included the study of trend and peculiarities of morbidity of separate nosological forms in the territories of the RF with high flood risk. By the statement of contents of retrospective epidemiological analysis the emphasis was focused on the process of epidemiological reasoning based on the conducted calculations. According to the analysis, there were stated the current precursory signs of the aggravation of the situation in both territories in the pre-flood period: AII morbidity ill-being, growth of salmonellosis morbidity (the Altai Republic), growth of infectious diseases of virus etiology, caused by rota- and noroviruses.

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INNOVATIVE TECHNOLOGIES IN THE MEDICAL DEMOGRAPHIC ASSESSMENT OF PUBLIC HEALTH

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Classical elaboration of medical demographic indexes of public health across administrative territories often does not allow to use them for the purpose of diagnostics of influence of negative factors on population, but their indicative properties significantly increase by "regional" analysis. Modern systems of monitoring of natural population movement implying information and communication technologies allow to considerably expand research possibilities and to perform the analysis in the eksadministrative-territorial zones intentionally formed according to a particular factorial characteristic.

Key words: public health, demography, information technologies in medicine.

By the end of the 1970s in the "Research institute for complex problems of hygiene and occupational diseases" of the Siberian branch of the RAMS there had been elaborated the method of social-hygienic classification of administrative territories on the level of oblast, region, city and district. The field works based on the stated method following in the 1980s allowed to reveal both common patterns of the development of public health of Siberian territories and their peculiarities. The first social-hygienic passport was created by the Institute in 1981 for Altai Krai, and it was 13 years before the well-known Government Resolution on the creation of the federal system of social-hygienic monitoring (№1146 of 6 October 1994).

By the performance of the social-hygienic monitoring the medical demographic component of the assessment of the state of public health is the main one. In the end of 1980s we elaborated the method of retrospective medical demographic diagnostics of public exposure to radioactive precipitations by nuclear tests and the assessment of the further losses of public health. Exactly on the basis of longitudinal medical demographic researches there were determined and evaluated the consequences of long-term nuclear explosions for the health of Altai Krai population.

At the same time it became clear, that the classical elaboration of medical demographic indexes of public health across administrative territories often does not allow to use them for the purpose of diagnostics of influence of extreme factors on population, but their indicative properties significantly increase by "regional" analysis, in the eksadministrative-territorial zones (EATZ) intentionally formed according to the degree of radiation effect. The search of the peculiarities of formation of mortality of separate birth cohorts of population in the eksadministrative-territorial zones is even more sensitive and allowed to obtain the most statistically significant indicators of the radiation trauma of population.

However, the achievement of this result required an intensive work of all 14 laboratory workers during 8 months (coping of the necessary information, its grouping and statistical processing, analysis).

Thus, already in the 1990s we stated the problem and together with the Altai regional medical information analytical center elaborated the automatic informational system "Smertnost" (mortality) (AS "Smertnost") being the personified register of all deceased persons, whose death is registered in the Civil Registry Office of Altai Krai.

At the present time, the base of the informational system contains more than half-million records. The program allows to perform the calculation of the whole complex of analytical indexes of mortality: intensive and extensive, gender, age, territory and place of death, and also indexes of time series with the determination of welfare degree (according to the specially developed method), standardized indexes, synthetic characteristics of mortality at the working age, average life expectancy (according to the method of Korchak-Cheprukovsky). Monthly seeding of the database allows to conduct the monitoring of mortality across the territory of the whole region and use it in the operative administration, primarily in the service of childhood and obstetrics.

For this purpose there were elaborated the forms of statistical tables joined into a bulletin, which is monthly presented to all interested users. AS "Smertnost" allows to shortly form the lists of deceased for at any period of time of various pathology both generally across the region and separate territories (cities, districts). The formed long-term electronic databases of mortality possess both practical and high scientific interest. Since 2002 on their basis there have been issued official statistical compilations of mortality of Altai Krai population. Moreover, the personified database allows to perform various types of analysis in short terms.

We conducted the research aimed at testing the possibilities of analysis of population state

of health outside administrative territorial borders by continuous statistical observation. The subject of the research was the mortality of population leaving in the conditions of poor access to medical help conditioned by geographical and infrastructural peculiarities.

Thus, Altai Krai includes several rural districts, the territory of which is crossed by the Ob River dividing the districts into two unequal parts: the large one with the district center, transport and social infrastructure, and the smaller one with only several settlements left, the residents of which live in the conditions of lesser access to medical help. Thus, there is formed the territory of residence of a part of population on the right bank of the Ob river, whose health characteristics in the known conditions of low access to medical help can be studied and compared with the health state of the left bank population.

Materials and methods

Out of the mortality data base there were selected all mortality cases with the characteristics of the deceased, who had one of the locations of the examined territories during the 3-year period of time marked in the section "permanent place of residence" and for whom there were calculated the values and indexes necessary for the analytical tables and their graphical reproduction. The labor costs of one scientific worker constituted one working day.

Results and discussion

It was stated, that the level of mortality among the population of the right bank (RB) in the conditions of respectively low access to medical help is higher, than among the population of the left Ob bank (LB), Table 1.

Table 1

Mortality of the population living on the left bank (LB) and right bank (RB) of the Ob River

Disease type	per 100 thous.		m		t	RB>LB %
	LB	RB	LB	RB		
Respiratory diseases	1,5	3,4	0,1	0,6	2,8	117,8
Circulatory diseases	10,6	13,2	0,2	1,3	2,1	25,3
Casualties, traumas	2,4	3,4	0,1	0,6	1,5	39,9
Neoplastic diseases	2,3	2,3	0,1	0,5	0,0	-0,7
General total	18,5	23,1	0,3	1,6	2,8	25,2

The influence of territorial and infrastructural peculiarities on the mortality is most significantly observed by the comparative evaluation of the index of seasonal fluctuations. Thus, by the absence of expressed seasonality of general mortality in the LB group there are registered strongly pronounced peaks of mortality during the winter period in the RB group. Even more pronounced is the seasonality of cardiovascular mortality.

Consequently, the reduction of the access to medical help can increase the population mortality by 25%, especially due to respiratory diseases – by 2,3 times, and circulatory diseases – by 1,3 times.

In 2011-2012 on the basis of AS "Smertnost" there was elaborated and implemented the modern system of monitoring of the natural population movement "Meddem". The software allows to form a medical certificate by means of input of the necessary information and further printing of the document. Simultaneously with the created document all the information from it is sent to the common regional data base. The expert part of the system allows to form basic data output for the analysis and monitoring of the processes of birth and mortality with the set of tables and lists. The application allows to form the main documents registering the natural population movement (cases of birth

and mortality). The user can be either a doctor registering the case of birth or mortality and issuing the certificate or a medical record administrator who only put the necessary information into the database and prints the document. The system saves input and output data of the system of registration and analysis of the natural population movement changing the process inside. All the information for monitoring and analysis of the natural population movement as a result of the web-application performance is available immediately at the moment of the certificate execution and issuing. The formation of the list of born and deceased in the form of a table allows to implement the methods of data processing by means of OLAP-technologies or any other means of working with electronic tables.

The created informational system allows to use medical demographic methods of research of the patterns of public health formation outside the frames of administrative territorial division in the eksadministrative-territorial zones initially formed according to any factorial characteristic.

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ANTI-INFLAMMATORY ACTIVITY OF GALIUM VERUM HERB INFUSION

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There was studied the anti-inflammatory activity of Galium verum herb infusion on the model of carrageenan edema of rats inflammation. In the conditions of long-term prophylactic administration, the infusion of the bedstraw has an inhibitory effect on the development of edema. The phlogolytic activity of Galium verum herb is associated with the presence of coffee acid. Coffee acid has the ability to remove active forms of oxygen and prevent a number of cellular biochemical reactions that ensures an inflammatory process.

Key words: Galium verum herb, anti-inflammatory activity.

Among the plants of Altai flora the plant genus Bedstraw (*Galium* L.) of madder family (Rubiaceae) is of considerable interest. For a long time, many of its species have been used in folk medicine as diuretic, anti-inflammatory and bactericidal agents for the treatment of gastro-intestinal tract and kidney diseases [1]. *Galium verum* contains anthracenederivative groups of alizarin in rootstocks and roots, the grass contains phenolcarbonic acids, flavonoids, coumarins, tanning agents, iridoids and steroidal saponins [2]. Consequently, topical is the search of new effective nontoxic drugs on the basis of plant sources for the treatment of inflammatory diseases of various etiology.

Objective: to study the influence of *Galium verum* herb infusion on the course acute inflammatory process in rats.

Materials and methods

The experiment were conducted on 20 outbred rats of both sexes weighing 200 – 220 g in accordance with the good laboratory practice (ПД3), the order of the Ministry of Health of the Russian federation # 708H from 23.08.2010, Guidance for pre-clinic drug studies conduction [3].

Anti-inflammatory activity was studied on the model of acute inflammation after the two-week intake of *Galium verum* herb infusion in the earlier specified optimal dose 1,5 ml.

The last infusion intake was made 1 hour before the phlogistic injection. Nimesulide in the dose of 10 mg/kg was used as a comparative drug.

Acute exudative inflammation was induced by subplantarily intake of 0.1 ml of 1% carrageenan solution [3]. The measurement of size of the right hind limb was made by plethysmometer after the course of *Galium verum* herb infusion before intake and also after 60 (1 hour), 120 (2 hours) and 240 (4 hours) minutes after phlogistic injection. The rate of anti-inflammatory activity was counted according to the data of the average growth of animal limbs obtained as the result of three parallel measurements.

Ehe drugs are considered effective, when their anti-inflammatory activity is over 39% [4].

The statistical processing of the obtained results was carried my means of calculation of sample mean (M) and error of mean (m) using the parametric Wilcoxon-Mann-Whitney test. By calculation the program Statistica 6.0. for Windows was used. The differences were considered significant at $p < 0,05$ [5].

Results and discussion

The development of aseptic inflammation caused by carrageenin includes several stages. In the first stage, (10-20 minutes) in response to the damaging effect of phlogogen, biogenic amines (serotonin and histamine) are released, activating the kallikrein-kinin system, which leads to the accumulation of kinins (1 – 2 hours). The latter facilitate the local release of hydrolytic enzymes of lyzosomes, stimulating the formation of prostaglandins, being the intermediates of the late stage of inflammation developing by carrageenan edema in 3 hours. Thus, the maximum of prostaglandin E_2 concentration is registered in 12-24 hours. Further, the system of compliment is included in this chain, functioning in complex with kinin system and blood coagulation system [6]. A number of authors often combine the mentioned late stages into one, and the carrageenan edema is considered as a two-stage process, the second stage of which is the result of release of prostaglandins, lyzosomes, bradykinin and proteases [7].

In course of the experiment the intake of 1% carrageenan solution by control animals lead to quick and consistent edema development. In these conditions long-term preventive intake of *Galium verum* herb infusion weakened its development.

At the early stages of edema development, the maximum effect of inflammation suppression under the influence of comparative drug – nimesulide – constituted 47%, while the effect stayed consistently high during the whole period of observation.

Table 1

The influence of Galium verum herb infusion on the development of carrageenan inflammation in outbred white rats

Animal group	Dose, mg/kg, ml/kg	Number of animals	Average growth of limb mass (X±m), %	Suppression of edema at the peak of inflammation, %
Control	-	10	39,8±4,3	-
Nimesulide	10	10	21,9±5,1*	47
Galium verum herb infusion (1:10)	1,5	10	27,3±6,8*	37

The effect of Galium verum herb infusion reached statistically significant results in one hour after the carrageenan injection, reaching maximum in 2 hours and weakened by the end of the experiment. In the period of maximum phlogolytic activity the Galium verum infusion suppressed the inflammation by 37%, which exceeds the anti-inflammatory activity in comparison with the control group by 1,5 times.

The study of the anti-inflammatory activity of Galium verum herb infusion is based on the current literature data on the phlogolytic activity of single polyphenols contained in the plant. The anti-inflammatory activity of the coffee acid contained in Galium verum infusion is connected with the ability to destroy reactive oxygen intermediates and prevent a number of cell biochemical reactions, ensuring the inflammatory process, which has a distinct protective effect on the capillary permeability [8].

Considering the stage nature of acute carrageenan edema and the registered maximum of activity during the period of energetic edema growth, the effectiveness of coffee acid can be explained by the interference in the trigger mechanisms of inflammatory process with the suppression of its vascular component in the alteration zone.

Conclusion

Consequently, the model of acute exudative inflammation allowed to reveal the influence of Galium verum herb infusion on one of the pathogenetic inflammation stages – stage of exudation, which opens the prospective for the complex study of Galium verum material.

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EFFECTS OF DRUGS INCREASING INSULIN SENSITIVITY ON PLASMA LEVEL OF URIC ACID AND URINE ACIDITY IN RATS DURING EXPERIMENTAL URATE NEPHROLITHIASIS

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The purpose of this study is to evaluate the influence of metformin, dapagliflozin and pioglitazone on the urine pH level and plasma level of uric acid during preventive and therapeutic drug administration in experimental urate nephrolithiasis. Subjects and methods. To form urate nephrolithiasis we used earlier repeated classic model of uricase inhibition that causes hyperuricemia in rats. We used metformin, dapagliflozin and pioglitazone as drugs increasing insulin sensitivity. At the end of the experiment we measured the urine pH level and UA level in the blood of rats after their decapitation. Results. Long-term preventive administration of metformin and pioglitazone during experimental urate nephrolithiasis allows to increase the urine pH level. Dapagliflozin causes the reduction of the urine pH level regardless of the type of drug administration. Both types of metformin, pioglitazone and dapagliflozin administration to experimental animals significantly reduce plasma level of uric acid in.

Key words: metformin, dapagliflozin, pioglitazone, experimental urate nephrolithiasis, prevention, therapy.

Urate nephrolithiasis is a pathological process developing as a result of a purine metabolism disorder leading to hyperuricemia and hyperuricosuria with uric acid (UA) crystals depositing in the kidneys. At the same time the chemical nature of urate concrements allows them to fully dissolve under the influence of certain physicochemical factors [1]. Pharmacological modulation of such factors can contribute to effective and safe litholysis of urate calculi therefore it is of great current interest.

Today there is no denying the fact that urate nephrolithiasis is related to the metabolic syndrome (MS) [2]. According to the statistics urate nephrolithiasis develops in 21.9% of MS patients and in 4.1% of patients without MS [3]. When studying specific features of the pathogenesis of MS it was found that there is insulin-dependent urine acidification that triggers urate calculi formation. Moreover, it is known that one of the main factors contributing to the formation of urate microlites is urine acidification and hyperuricemia [4].

Taking the above into consideration, we suggested that administration of drugs increasing insulin sensitivity can lead to alleviation of factors being conducive to urate calculi formation.

Objective: the purpose of this study is to evaluate the influence of metformin, dapagliflozin and pioglitazone on the urine pH level and plasma level of uric acid during preventive and therapeutic drug administration in experimental urate nephrolithiasis.

Materials and methods

We studied 102 male Wistar rats weighing 220-310 g. The animals were placed in single cages adapted for urine collection. Laboratory animal care was organized according to the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

To form urate nephrolithiasis we used earlier repeated classic model of uricase inhibition that causes hyperuricemia in rats [5].

We used metformin, dapagliflozin and pioglitazone as drugs increasing insulin sensitivity.

Synthetic antidiabetic drug metformin (biguanide derivative) increases insulin sensitivity by increasing affinity of insulin receptors, by their conformational changes and by stimulation of the pathway at the receptor and post-receptor level [6, 7].

Dapagliflozin, a representative of a new class of oral sodium-glucose co-transporter 2 inhibitors, compensatively increases sensitivity of insulin receptors in association with reduction of renal glucose reabsorption by inhibiting SGLT2 in epithelial cells of renal tubules [7].

Pioglitazone, a thiazolidinedione derivative, increases the number of insulin receptors on the cell membrane by activating PPAR- γ nuclear receptors [7, 8].

Experimental animals were provided with two types of drug administration: preventive and therapeutic. All the drugs were administered intragastrically in the form of 2% starch mucilage.

The daily doses (Table 1) were calculated according to the interspecies scaling formula with reference to human therapeutic doses [9].

During studying of the potential of each of the drugs animals were divided into 3 groups. The control group was provided with 20 g of standard laboratory nutritional mixture including 500 mg/kg of oxonium acid and 1000 mg/kg of UA daily during 3 weeks. The second group («Prevention» group) was also provided with preventive oral drug administration during the same period of time. Animals from the third group («Therapy» group) were provided with the drug in the same dose from 11th to 21st day of the experiment.

At the end of the experiment we measured the urine pH level and UA level in the blood of rats after their decapitation.

Doses of drugs changing insulin sensitivity

Substance	Human daily dose, mg/kg	Rat daily dose, mg/kg
Metformin	12.5	150.0
Dapagliflozin	0.125	0.7
Pioglitazone	0.375	2.2

For statistical analysis we used Microsoft Office Excel 2003 (Microsoft Corporation, USA) and Sigma-Stat 3.5 (Systat Software Inc., USA). The Kruskal-Wallis test by ranks was employed for comparison between the three groups. The nonparametric Mann-Whitney U test was used for post hoc pairwise comparison. All values are specified as a median and an interquartile range: Me (25%; 75%). A calculated difference of $p < 0.05$ was considered statistically significant [10].

Results and discussion

The experiment showed that both preventive and therapeutic drug administration of metformin significantly improves the course of urate nephrolithiasis. It appeared that together with long-term drug administration there also took place the reduction of plasma level of UA: in the control group it was 1.4 (1.2; 1.8) mg/dl, in the "Prevention" group – 1.1 (0.8; 1.2) mg/dl ($p = 0.009$ in comparison with the control group), in the "Therapy" group – 1.0 (0.7; 1.2) mg/dl ($p = 0.013$ in comparison with the control group).

As a result of long-term administration of dapagliflozin plasma level of uric acid significantly lowered in the "Prevention" group and in the "Therapy" group in comparison with the results in the control group by the end of the follow-up period: 1.3 (1.1; 1.8) mg/dl in the control group, 0.8 (0.7; 1.0) mg/dl ($p = 0.006$ in comparison with the control group) in the "Prevention" group, 0.7 (0.6; 0.8) mg/dl ($p = 0.005$ in comparison with the control group) in the "Therapy" group.

Both preventive and therapeutic administration of pioglitazone to animals with experimental urate nephrolithiasis caused the reduction of plasma level of UA in experimental animals in comparison with the control group: 1.3 (1.1; 1.5) mg/dl in the control group, 1.1 (0.9; 1.1) mg/dl ($p = 0.007$ in comparison with the control group) in the "Prevention" group, 0.9 (0.8; 1.1) mg/dl ($p = 0.002$ in comparison with the control group) in the "Therapy" group.

The obtained results prove that metformin, dapagliflozin and pioglitazone do not only interfere into glycometabolism but also influence other types of metabolism including purine metabolism [11].

Table 2

Urine pH levels in experimental urate nephrolithiasis rats

Group	Metformin	Dapagliflozin	Pioglitazone
Control	6.8 (6.5; 6.9)	6.8 (6.5; 6.9)	6.8 (6.6; 7.4)
Prevention	7.9 (7.5; 8.2)	6.1 (5.9; 6.2)	7.8 (7.5; 8.6)
Therapy	7.0 (6.6; 7.4)	5.9 (5.3; 6.6)	7.5 (7.2; 8.0)
Kruskal-Wallis test			
p	0.003	0.003	0.011
Mann-Whitney U test			
p, "C" and "P"	0.002	<0.001	0.013
p, "C" and "T"	0.102	0.037	0.058
p, "P" and "T"	0.030	0.732	0.064

Note: p – level of statistical significance. "C" and "P" - the control group in relation to the "Prevention" group; "C" and "T" - the control group in relation to the "Therapy" group; "P" and "T" - the "Prevention" group in relation to the "Therapy" group.

Taking into consideration the importance of pH level changes in the pathogenesis of urate nephrolithiasis it should be noted that metformin and pioglitazone caused the urine alkaline pH-shift in comparison with the control group, which was significant in the "Prevention" group and tended to appear in the "Therapy" group (Table 2).

As noted above, insulin resistance plays an important role in urinary acidification. It is known that by activating its own receptors in the renal tubules insulin stimulates $3 \text{ Na}^+/\text{H}^+$ transferase isoform which provides direct transportation of NH_3 to the renal tubular lumen [12]. Thus, insulin resistance leads to the reduction of ammonium production and secretion - processes contributing

to urinary acidification. Apparently, by increasing insulin sensitivity of insulin receptors in the renal tubules metformin and pioglitazone make $3 \text{ Na}^+/\text{H}^+$ transferase isoform active and consequently activate transportation of NH_3 to the renal tubular lumen leading to the increasing of the urine pH level that must be admitted as a positive effect.

However, it should be noted that both preventive and therapeutic dapagliflozin administration (as it appears from Table 2) led to the certain urine acidic pH-shift in comparison with the control group: 10% pH-shift in the "Prevention" group, 13% pH-shift in the "Therapy" group. This result that seems to be unexpected can be explained in the following way. It is known that dapagliflozin administration results in reduction of sodium and glucose co-reabsorption in the renal tubules caused by direct renal inhibiting of glucose co-transporter SGLT2. It leads to the increase in the level of sodium ions in the proximal renal tubules and to the compensatory activation of mechanisms regulating their reabsorption in more distal parts of the renal tubules. It is known that a Na^+/H^+ transferase plays an important role in the regulation of urine acidity. It is located on the apical membrane of an epithelial cell in the descending portion of the proximal tubules and it provides reabsorption of sodium ions into the cell in exchange for protons, which appear in the urine as a result of carbonic acid disintegration [13]. When the level of sodium ions in the liquid from the upper portions inside the tubule increases the transferase starts to function more actively and in spite of the working ammonium buffer it leads to the urine acidic pH-shift. It is not improbable that the reduction of the urine pH level is the result of systemic euglycemic ketoacidosis that can develop in conditions of selective SGLT2 inhibition in response to dapagliflozin [14].

Conclusion

Long-term preventive administration of metformin and pioglitazone during experimental urate nephrolithiasis allows to increase the urine pH level and this is an important positive effect. Dapagliflozin causes the reduction of the urine pH level regardless of the type of drug administration. Both types of metformin, pioglitazone and dapagliflozin administration to experimental animals significantly reduce plasma level of uric acid in rats and it is an important positive feature irrespective of the urine pH level.

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DIROFILARIASIS. HUMAN AS A SECONDARY DEFINITIVE HOST (CLINICAL CASE)

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*In recent decades, cases of dirofilariasis have become more frequent in Russia. From 1996 to 2001, 152 cases of invasion were identified. In the temperate climate zone, the authors first established the case of sexual reproduction of *Dirofilaria repens* in a human body. The article describes the clinical cases of dirofilariasis in Altai Krai.*

Key words: dirofilariasis, invasion, *Dirofilaria repens*.

Recent years in Altai Krai have been marked by an increase of human cases of dirofilariasis— an obligate-transmissible dog helminthiasis caused by *Dirofilaria repens*. In the Russian Federation, the disease had long been considered rare. Since the middle of 1990s of the XX century, there has been observed an increase of the number of registered dirofilariasis cases in human and the growth of attention to this problem. For the period of 1996 – 2001, there had been registered 152 cases, primarily in the residents of endemic territories of the South [1].

However, the analysis of morbidity of the recent years showed that a particular frequency of the disease is present in the regions with moderate climate (Moscow, Tula, Ryazan, Lipetsk Oblasts, the Urals, The Republic of Bashkortostan, etc.). The disease was also registered in Saratov, Samara and Nizhny Novgorod Oblasts, the Republic of Kalmykia. By the beginning of 2014, there had been registered 850 *D. repens*-infested people on the territory of 42 entities of the RF [2]. The hotbeds of invasion in the zone of moderate climate are determined up to 55–57°N (twenty years ago the Northern border was considered 53–54°N) [3]. Thus, at the present time, there is a tendency not only to the increase of the stated pathology, but also to the broadening of its areal to the Northern regions, which is probably connected with the rise of the average annual temperature.

In Altai Krai dirofilariasis has been registered since 1989. For the period from 1989 to 2011, there were detected 39 cases. Over the last 10 years, dirofilariasis morbidity grew nearly by four times. Thus, from 1989 to 1998, there were registered 8 cases, from 1999 to 2011 – 31 case [4], which can be considered as an outbreak of the disease on the territory of Altai Krai.

People become infected with dirofilariasis by agricultural works, during outdoor recreation from May to September, in the places with considerable populations of mosquitos and infected animals [1].

Dirofilariasis is caused by the class of filarial nematodes (roundworms), order Spirurida,

suborder Filariata, superfamily Filariidae, genus *Dirofilaria*. The agents of invasion in the territory of the Russian Federation *D. repens* and *D. immitis* are obligate parasites of the carnivorous families of Dogs and Cats, *D. ursi* of the brown bear and the Amur tiger. Mature females *D. repens* reach the body length of 135-150 mm, *D. immitis* – 180-300 mm, *D. ursi* – 120-225 mm. Males, respectively, reach 50-58 mm, 100-110 mm, 51-85 mm. Larval stages – microfilariae – without a cap, with a blunt front end, pointed and filiform back end. The length of microfilaria – 0,30-0,36 mm, the width – 0,006-0,008 mm (comparable to the erythrocyte diameter).

Dirofilarias, after the period of larvae migration through the blood channel, go through the stage of deposit in liver and spleen, which continues up to half a year, then settle in the subcutaneous connective tissue of dogs or, in case of larval penetration, into a secondary optional host – human. The carriers of microfilariae of the helminths of Filariidae family are mosquitos of *Culex*, *Aedes*, and *Anopheles* genera. On the territory of the region there are indicated 25 species of mosquitos carrying dirofilarias, including 17 species and 2 subspecies p. *Aedes*, 1 species and 3 subspecies p. *Culex*, 1 species p. *Anopheles* (*maculipennis*). The dominating species are p. *Aedes*: *A. communis* *A. vexans* [4]. According to modern concepts, human is an optional dead-end host of the parasite, as females do not reach maturity in the human's organism, sexual reproduction does not occur and microfilariae do not sprout into the blood.

However, in recent years, there have appeared separate works denoting the fact, that the possibility of microfilaremia cannot be totally excluded. The sources of literature describe the cases of larvae occurrence in human blood. V.G. Supryaga and coauthors (2004) were the first to detect in the territory of Russia (Vladimir and Samara Oblasts) the patients with microfilariae in the punctate of the subcutaneous tumor [5-7].

Dirofilariasis is met in persons of both genders, in the age groups from 3 to 75 years. In human, mature forms of filariae localize in the area

of limbs, low neck zone, under the skin of eyelids in the subcutaneous connective tissue. There are described the cases of migration of parasites under the skin in the area of head – neck – upper limbs, which is the sign of «larva migrans cutanea» phenomenon.

The first manifestation of the disease is the appearance of a painful tumor, the area of which can be characterized by pruritis or urtication of various intensity. In some cases there can be observed headache, nausea, fatigue, high temperature. Eosinophilia of peripheral blood is not typical of dirofilariasis, but in several cases it can constitute 8-11%. The optimal method of treatment – surgical resection of the focus of chronic inflammation together with the helminth, around which there can form a connective-tissue capsule [8, 9].

Clinical case. In April 2014 the 56-year-old female patient N. was admitted to the Department of bone skin and soft tissue tumors №2 of the FS-BHI AROH with complaints of the tumor in the left breast, which she had found in November 2013. At the same time she had pains in the area of the tumor, which became less intensive in 1,5 months and were registered only by pressing.

Objectively: by observation of the area of the left breast, on the border of lower quadrants, there is observed a postoperative scar, 0,3*7sm (in 1999 - sector resection for fibroadenoma). By palpation the scar is soft, atrophic, in its projection there is determined a tumor of 3sm in diameter of firm texture with indistinct boundaries, soldered by surrounding tissues, moderately painful by pressing. No nipple discharge. Regional lymphatic nodes not distinctly palpated.

Mammography of 27.02.2014 - on the border of lower quadrants, there is observed an area of stroma induration with indistinct boundaries of inhomogeneous structure, size 3,5*2sm. Conclusion: Nodular fibrosis, suspected left breast cancer.

Ultrasonic examination of breast of 06.03.2014 - on the border of lower quadrants in the projection of the postoperative scar, there is located a hypo-isoechoic round inhomogeneous formation with a distinct wavy border, size 23,4*16,9*20,0mm, with a visible blood flow in the center and peripherally by CDI. Conclusion: Suspected left breast cancer.

Thin-needle aspiration biopsy of the left breast tumor of 26.02.2014.

Cytological conclusion – signs of purulent inflammation, macrophages, cubical epithelium cells.

Diagnosis before surgery: Chronic mastitis. Suspected left breast cancer.

The patient is planned to undergo sectoral resection of the left breast with the urgent histological test, by cancer diagnosis – Madden's mastectomy.

By the urgent histological test during the operation there was detected a parasite, presumably, dirofilaria.

Macroscopic examination – the sector of breast tissue 5,0x3,0x3,0 sm, on the section – cyst cavity with yellowish fluid, in the center – a filiform white circinated formation, by touching with forceps – active movement. By expansion – the formation 3,5 sm long, diameter – 1,0 mm, one of the ends is clublike thickened up to 2,5 mm. The mature helminth was resected together with the connective tissue membrane of the capsule and cyst cavity.

Consultation by the specialist of the clinical laboratory diagnostics - *Dirofilaria repens*.

Pathomorphological examination – the internal capsule surface is presented by granulation tissue with a large number of lymphocytes. The fibrous part of the capsule includes the breast tissue with focal plasma cell infiltration and separate granulomas surrounded by fibrous tissue with single foreign body giant cells. Inside granulomas there are observed assemblies of microfilariae (longitudinal and cross sections) (Figure 1).

Final clinical diagnosis – dirofilariasis of the left breast. Mature and larval stage. State after surgical treatment.

After further curation of the patient it was stated, that the tumor did not relapse. No return visits for operative treatment were registered. The lack of neoplasm recurrence allows to assume, that the observed microfilariae had been formed as a result of *Dirofilaria repens* sexual reproduction.

In March 2017 in Altai Krai, there has already been registered two cases of dirofilariasis. Female patient P. from Kamen-na-Obi, 1959 year of birth, was admitted to FSBHI "Altai Regional Clinical Hospital" with a helminth localized in the right region of the neck (Figure 2). Helminth was resected and identified as *Dirofilaria repens*. Biopsy with further microscopy of surrounding tissues was not conducted. Final clinical diagnosis – dirofilariasis of the right region of the neck.

Patient N. applied to the "Pavlovsk Central District Hospital" with a formation on the front surface of the abdominal wall accompanied by itching and compression. Provisional diagnosis – lipoma of the front surface of the abdominal wall. By operative treatment there was resected a capsulated helminth of white color more than 3 sm longwise, which was also identified as *Dirofilaria repens*. Biopsy with further microscopy of surrounding tissues was not conducted. Final clinical diagnosis – dirofilariasis of the front surface of the abdominal wall.

Both cases of dirofilariasis are local. The patients did not leave the territory of Altai Krai during the recent year, in summer they were exposed to mosquito bites. The patients applied for medical help in several months since the disease onset.

By the first reference to a doctor, the established diagnosis was not connected with parasitic etiology.

According to our observations and the literature data, the majority of patients apply for med-

ical help on the subject of subcutaneous tumors disturbing them for several days or even months during spring (March – May).

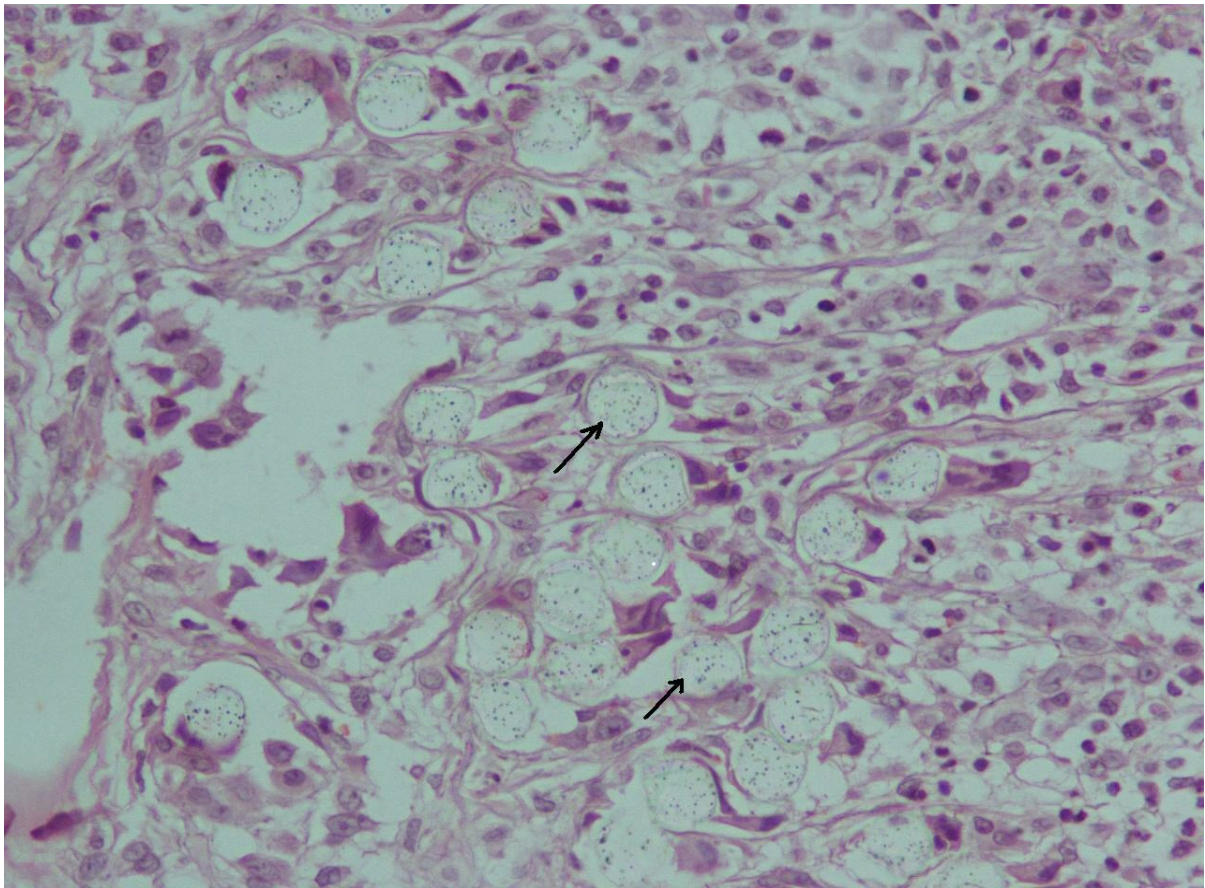


Figure 1.
Cross sections of microfilariae inside granulomas in the breast tissue



Figure 2.
Helminth in the right region of the neck

Unfortunately, nowadays the monitoring of animal (dog) dirofilariasis morbidity is not carried. Thus, the "Barnaul Animal Health Center" does not possess statistical information on the dirofilariasis morbidity among dogs after the first outbreak in the 1990s of the XX century. The degree of prevalence of the disease in dogs of Altai Krai, in which dirofilariasis is a serious disease affecting not only subcutaneous fat, but also heart, is unknown. Consequently, it does not seem possible to estimate the possible risks for human health.

Conclusion

The case of *Dirofilaria repens* sexual reproduction in human organism was firstly established within the boundaries of the Siberian region (Altai Krai) in the zone of moderate climate. On the basis of possible inclusion of human in the group of secondary definitive hosts of *Dirofilaria repens*, it is recommended to revise the principles of transmissible invasions (filariasis) prevention on the territory of Altai Krai from the perspective of interruption of the invasion transmission – extermination of mosquitoes, detection and dehelminthization of pets, prevention of mosquito contact with pets and human.

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ATHEROSCLEROSIS OF THE CORONARY ARTERIES AND DISORDERS OF THE HEMOSTATIC SYSTEM

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For many decades coronary heart disease has retained the first place in the structure of mortality from cardiovascular diseases in Russia (49.9%). Disturbances in the hemostatic system form a permanent hypercoagulable state, which, against the background of atherosclerosis, can lead to thrombotic complications. This article presents the results of a study of the features of the hemostatic system, endothelial cell markers and the carriage of thrombogenic polymorphisms in patients with coronary heart disease at different levels of atherosclerotic lesion of the coronary arteries.

Key words: ischemic heart disease, hemostatic system, atherosclerosis.

Cardio-vascular diseases (CVD) are the most frequent mortality factor (in the RF – 49,9%, 2014), the first position among which has been for many years occupied by the ischemic heart disease (IHD) including its acute and chronic forms [5, 11]. It is known, that an important role in the development of atherosclerosis as the main cause of IHD is played by the disorders of the hemostatic system, moreover, the process involves all the components of the coagulation system [2, 16, 17]. There is formed the constant hypercoagulation state predisposing to the development of thrombotic complications associated with atherosclerosis. In these circumstances, the main risk is not atherosclerosis itself, but the artery thrombosis accumulated on it and leading to acute ischemia of vital organs and often having lethal outcome [10]. In patients with macrofocal myocardial infarction (MI), thrombosis of coronary arteries (CA) is registered in 95-97% of cases [3, 4, 8]. These processes can be determined both by genetic defects by congenital thrombophilia and by the result of the effect of external environment unfavorable factors and numerous diseases. Thrombophilia itself increases the risk of thrombosis, and its significance can be considerably increased in combination with other risk factors [9, 15]. In recent ten years there have been not only identified the genetic roots of the majority of congenital pathologies, but there have been also found the candidates of the sweeping majority of acquired diseases including thrombogenic polymorphism and mutations determining the genetic predisposition to the intensive thrombogenesis [7, 12, 14, 18]. At the same time, some mutations, e.g. in the gene of VII, XIII factor, according to several authors, can reduce the risks of thrombosis (MI) even by expressed coronary atherosclerosis [1, 6, 13].

Objective: To study the parameters of the hemostatic system, markers of endotheliosis and thrombogenic polymorphism in patients with IHD in comparison to the control group. To study the peculiarities of hemostatic system, markers of endotheliosis and thrombogenic polymorphism in patients with IHD by the different level of CA atherosclerotic disease.

Materials and methods

Using the method of random sampling, the main group included 130 men with coronary heart disease, average age - $50,8 \pm 10,4$. The control group included 39 healthy men, average age - $47,5 \pm 3,8$ ($p=0,06$). In both groups, there were evaluated 16 parameters of the hemostatic system, 3 markers of endotheliosis and thrombogenic polymorphism by 12 parameters. The exclusion criteria for both groups: acute coronary syndrome (ACS) as the cause of the current hospital stay, oncology, concomitant pathology at the decompensation stage, inflammatory diseases, surgical interventions during the last 6 months. In both groups, there were evaluated 16 parameters of the hemostatic system, 3 markers of endotheliosis and thrombogenic polymorphism by 12 parameters. Further, the main group was divided into subgroups depending on the level of the coronary arteries injury, which were compared to each other: I ($n=35$) – single-vessel disease (myocardial infarction (MI) in the medical history – 71,4 %), II ($n=32$) – two-vessel disease (MI in the medical history – 78,1 %), III ($n=58$) – the multi- vessel disease of the coronary artery (CA) (MI in the medical history – 72,4 %), IV ($n=5$) – “clean” CA (MI in the medical history – 100,0 %). The statistical processing of the material was performed by means of Statistica 6.0 programs. By the presence of normal distribution the statistical significance of the differences and the implemented sample data was determined by means of Student t-test. For each value possessing normal distribution there are given mean values (M) and standard deviation (SD). The comparison of qualitative characteristics was conducted by means of contingency tables 2x2, the hypothesis testing was performed according to the Pearson's chi-squared test χ^2 . The differences were considered statistically significant by the probability of event $p \leq 0,05$.

Results and discussion

Patients with IHD (main group) in comparison with the control group showed the increase of the fibrinogen level ($p < 0,001$) and high molecular components of the fibrinogen pool (SFC)

($p=0,01$), the growth of activity of VIII factors ($p<0,001$) and Willebrand factors ($p<0,001$). Totally, it testifies the moderate activation of blood coagulation balanced by physiological anticoagulants. Thus, the SFC level in patients with chronic IHD was two times higher than its value in the control group, while the activity of anti-thrombin and C protein stayed normal. In patients with CIHD the time of XII-a dependent fibrinolysis activated through the triggers of the contact stage of blood coagulation and kinin-kallikrein system also turned out to be two times longer ($p<0,001$). Herewith, the amount of the fibrinolytic system substrate – plasminogen – turned out to be sufficient. Additionally, the endothelial dysfunction was present: elevated level of homocysteine (HC, $p=0,04$) and endothelin-1 (ET-1, $p<0,01$). According to our data, the difference of the aggregation activity of thrombocytes - adenosine diphosphate (ADP) and collagen ($p<0,001$) in the group of patients with IHD and the control group was connected with the intake of disaggregants. The study of frequency of thrombogenic mutations and polymorphism carriage in the compared groups showed, that in patients with IHD there is a significant prevalence of only Htzg genotype of A66G gene MTRR ($p=0,03$). The comparison of the hemostatic system parameters in patients of the subgroups with single- and multi-vessel CA disease demonstrated, that the significant difference is determined by SFC level ($p=0,03$), Willebrand factor ($p=0,03$) and the activity of VIII factor ($p<0,001$), which were higher by more severe CA disease (Table 1). By the comparison of the subgroups with each other and with the control group, the anticoagulant element and fibrinolysis did not show any differences, which evidences the retaining effect of anticoagulants and the fibrinolytic system in response to moderate thrombinemia registered in patients with IHD. The examination of thrombocyte aggregation in response to ADP, adrenalin and collagen showed, that the significant difference is observed between the subgroups of patients with single- and multi-vessel CA disease ($p\leq 0,01$). The comparison of the subgroups showed, that the two-component antiaggregant therapy was received by 52,8% of patients with single-vessel disease and 52,6% of patients with multi-vessel CA disease ($p=0,9$). By multi-vessel CA disease the aggregation of thrombocytes was the highest, while its studied parameters did not differ from the parameters of the control group despite the intake of disaggregants at appropriate dose. The stated fact can indicate the lower effectiveness of disaggregant therapy in patients with multi-vessel CA disease. The comparative study of thrombogenic polymorphisms showed, that in patients with multi-vessel CA disease the prevalence of Htzg A1298C genotype of MTHFR gene is higher (53,5%) than in the control group (28,2 %, $p=0,01$) and in patients with single-vessel (31,4 %, $p=0,04$), two-vessel CA disease (31,2 %, $p=0,04$).

It should be noted, that Hmzg genotype of G226A gene *F XIII* was rarer registered exactly in the subgroup with multi-vessel CA disease (3,5 %), while in the control group this genotype was met more often (15,4 %, $p=0,03$). This interesting fact can indicate the possible protective effect of Hmzg form carriage of this gene in the development of MI [1, 13]. As the current research has shown, out of 130 patients with IHD only 5 (3,8 %) lack the atherosclerotic CA disease. These 5 patients had undergone laboratory and instrumentally confirmed MI at a young age. The average age of patients with “clean” CA constituted $36,6\pm 2,6$ years.

In patients with “clean” CA in comparison to the patients with different CA disease there was observed the tendency to a higher concentration of the components of the fibrinogen pool (SFC) – $13,30\pm 6,22$ mg/100ml; the increase of the time of XII-a dependent fibrinolysis – $29,80\pm 14,65$ min and HC concentration – $14,52\pm 4,41$ μ mol/l (Table 1). All 5 patients showed the carriage of thrombogenic polymorphisms of the same gene – combination of Hmzg and Htzg forms of *PAI 1* genes and genes of the folate cycle (*MTR*, *MTRR*, *MTHFR*). Also, despite the presence of MI in the medical history, in all cases there is registered the presence of Hmtg and Htzg forms of *F XIII* gene, which indicates the lack of protective effect from MI of this gene in patients with “clean” CA. In our opinion, the obtained results differ from the data of literature, probably, because of the fact, that in our work “clean” CA by IHD are discovered only in young patients, but not in patients with systemic atherosclerosis and require further research. This is partially confirmed by the significantly lower frequency of Hmzg form of *F XIII* gene carriage in patients with multi-vascular coronary disease. All this invites the assumption, that at a young age MI is developed not as a consequence, but in contradiction to CA atherosclerotic disease.

In the current case, all five patients had coagulation disorders in the form of thrombinemia, disorders of the internal mechanism of fibrinolysis and high level of HC and ET-1. At the same time, these patients had an adequate response to the disaggregant therapy. According to the literature sources [3, 9], thrombophilia is characterized by: young age, thrombotic family history, changes in the hemostatic system in combination with the carriage of Hmzg or Htzg forms of thrombogenic genes. Consequently, the development of MI in patients with “clean” CA is determined by thrombophilia.

Conclusion

In patients with IHD there were discovered the signs of moderate thrombinemia and endothelial dysfunction, which are more expressed in patients with multi-vessel CA disease. In patients with multi-vessel CA disease the thrombocyte aggregation in response to ADP, adrenalin and collagen was much higher than in patients with one-vessel

Table 1
Comparative characteristics of the studied parameters of the hemostatic system and endothelial dysfunction in patients with IHD depending on the level of CA disease

Parameter	Main group (M±SD)				Control group n=39, (M±SD)	p1-2/1-3/1-4/2-3/ 2-4/3-4	p1-5/2-5/3-5/4-5
	«clean» CA n=5	single-vessel disease n=35	two-vessel disease n=32	multi-vessel disease n=58			
	1	2	3	4	5		
Thrombocytes, *10 ⁹ /k	250,00±59,78	233,89±61,80	241,82±48,68	218,75±55,38	249,66±49,03	0,5/0,7/0,2/0,6/0,2/0,06	0,9/0,5/0,7/0,1
APTT, s	33,60±3,50	33,41±3,81	33,35±4,62	34,15±5,81	35,02±2,03	0,8/0,9/0,8/0,9/0,5/0,5	0,03/0,02/0,04/0,4
Prothrombin time, s	12,40±1,23	13,38±2,36	13,96±3,18	13,27±1,29	13,36±1,26	0,1/0,3/0,4/0,4/0,7/0,1	0,1/0,9/0,3/0,7
Thrombin time, s	20,60±2,07	20,29±5,27	19,48±2,06	20,28±2,92	18,84±1,20	0,7/0,3/0,7/0,4/0,9/0,1	0,007/0,09/0,1/0,004
Fibrinogen, g/l	3,98±1,51	3,80±1,34	3,77±1,02	4,30±1,47	2,98±0,74	0,8/0,8/0,4/0,9/0,1/0,07	<0,001
SFC, mg/100 ml	13,30±6,22	8,27±5,19	8,57±4,83	11,05±6,33	6,01±3,94	0,06/0,06/0,4/0,8/0,03/0,06	<0,001/0,06/0,03/<0,001
D-dimer, ng/ml	113,20±109,40	104,73±86,45	124,22±99,90	122,75±99,42	68,23±29,89	0,7/0,6/0,7/0,4/0,4/0,9	0,04/0,01/0,001/0,001
III antithrombin activity, %	108,20±8,89	106,94±10,89	109,00±10,60	99,91±10,66	108,79±9,23	0,6/0,8/0,09/0,4/0,003/<0,001	0,9/0,4/0,9/<0,001
Screening of disorders in the system of C, HO proteins	1,02±0,31	0,96±0,17	1,05±0,14	1,02±0,19	1,09±0,14	0,5/0,7/0,9/0,03/0,1/0,4	/<0,001/0,1/0,03
XII-a dependent fibrinolysis, min	29,80±14,65	25,00±14,54	22,25±10,83	26,52±13,99	14,35±9,26	0,2/0,1/0,3/0,4/0,6/0,1	<0,001
Plasminogen, %	132,20±29,50	119,45±20,04	117,09±121,36	117,80±22,17	114,48±15,82	0,2/0,2/0,2/0,6/0,7/0,8	0,04/0,2/0,5/0,4
VIII factor activity, %	168,20±27,95	159,33±37,65	166,58±30,25	181,40±21,75	131,41±38,24	0,6/0,9/0,2/0,4/<0,001/0,009	<0,001
Thrombocyte aggregation – ADP, %	47,80±18,63	48,03±8,36	51,83±16,04	58,61±17,18	64,35±17,93	0,9/0,6/0,2/0,2/0,001/0,07	<0,001/<0,001/0,003/0,1
Thrombocyte aggregation – ristomycin, %	82,66±10,69	82,00±14,28	74,77±26,44	82,73±19,64	86,90±7,81	0,9/0,4/0,9/0,4/0,9/0,3	0,3/0,2/0,02/0,3
Thrombocyte aggregation – adrenalin, %	18,50±11,67	29,32±19,11	32,38±24,34	43,02±24,73	36,64±28,20	0,3/0,3/0,06/0,6/0,01/0,1	0,2/0,2/0,5/0,3
Thrombocyte aggregation – collagen, %	46,00±28,43	40,12±24,65	44,00±26,39	55,15±19,62	65,17±20,87	0,5/0,7/0,1/0,6/0,02/0,07	0,1/<0,001/0,002/0,03
Willebrand factor, %	172,20±47,48	159,90±38,83	176,00±27,80	176,12±33,14	131,05±38,14	0,5/0,8/0,8/0,06/0,03/0,9	<0,001/0,002/<0,001/<0,001
Homocysteine, mkmol/l	14,52±4,41	13,37±7,01	13,76±5,62	13,60±5,63	9,86±2,22	0,7/0,8/0,7/0,8/0,8/0,9	<0,001
Endothelin-1, fmol/ml	0,48±0,12	0,71±0,68	0,81±0,71	0,86±1,13	0,26±0,02	0,5/0,3/0,4/0,5/0,5/0,8	<0,001

disease, despite the identical disaggregation therapy. The prevalence of Htzg genotype of the A1298C gene MTHFR in patients with multi-vessel coronary disease is higher (53,5%) than in the control group (28,2 %) and in patients with single-vessel (31,4 %) and two-vessel disease (31,2 %). Patients with “clean” CA constituted 3,8 % and had: MI onset at a young age, coagulation disorders in the form of thrombinemia, disorders of the internal mechanism of fibrinolysis and high level of HC and ET-1. In these patients there was registered the same type of thrombogenic polymorphism – the combination of Hmzg and Htzg gene forms PAI-1 and genes of the folate cycle (MTR, MTRR, MTHFR), which in complex with coagulation disorders and the absence of CA atherosclerotic lesions are the markers of thrombophilia.

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PREVALENCE OF CEREBRAL STROKE IN VARIOUS NATURAL ZONES OF THE REPUBLIC OF BASHKORTOSTAN

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There was studied the frequency of cerebral stroke in natural zones of the Republic of Bashkortostan, various prevalence can be determined by the ratio of minor elements and mineral composition of soils. The practical implementation of the research results is the creation of special zone maps indicating the degrees of cerebral stroke risk necessary for performance of early prevention.

Key words: stroke, natural zone, early prevention.

According to the World Health Organization, more than 6 million people annually die of stroke, in the Russian Federation, acute cerebrovascular events (ACE) occur in more than 500 000 people per year [4]. Upon that, the prognosis is often unfavorable, the mortality constitutes 34,6%, disablement – 20%, 56% get limited working capacity and only 8% return to their usual life [3]. There has been conducted several researches devoted to the zone division of Russian regions factoring in the prevalence of cerebral stroke and other neurological diseases, in which there were also revealed the differences in clinical course of disease depending on the geographical peculiarities of the territory [5]. There was determined the zonal distribution of disseminated sclerosis prevalence conditioned by the geological geomorphological structure of the territory in the Republic of Bashkortostan [1].

The prevalence of strokes can differ throughout various natural zones, there is also proved the influence of climatic, geographical and ecological features of the region on the development of stroke subtypes. The role of territorial climatic peculiarities on the prevalence of cerebral stroke is also confirmed by the studies of Kazakh researchers, who had determined direct relation between the frequency of strokes and the levels of temperature and humidity of the region [6].

Objective: to study the frequency of strokes in various natural zones of the Republic of Bashkortostan (RB).

Materials and methods

There were studied the data on ACE morbidity in RB regions based on annual reports of central district hospitals, primary and regional cardiovascular centers. Depending on the reference to a particular natural zone, 54 regions were divided into 6 groups [2]. The frequency of stroke occurrence was calculated for 100 000 population. The statistical data processing was conducted by means of STATISTICA 6.

Considering the fact, that there were studied the relations between a particular natural zone

and the frequency of ACE, urban settlements had been excluded out of the statistical processing, there was made the summation of regions with different economic development degree within the borders of one natural region.

Results and discussion

According to the cartographo-geodetic data, the Republic of Bashkortostan is divided into 6 natural zones: in the Russian Plain: forest zone (1 group), forest-steppe zone (2) and steppe zone (3), south-east – mountain-forest-steppe zone of the Bashkir Urals (4), trans-Ural forest-steppe zone (5) and steppe zone (6). Each natural zone differs by climatic, geological and hydrological features, and in the variety of plant and animal life [2].

Considering that the limits of RB administrative regions do not coincide with the borders of natural zones, the research was performed only in those regions, the territory of which is totally included into a particular natural zone.

It was stated, that in 2016 the average frequency of stroke occurrence in the 1st group constituted 282,6 per 100 000 population, in the 2nd group – 338,0; in the 3rd – 367,4; in the 4th – 252,4; in the 5th – 279,5; in the 6th – 214,3.

The highest frequency of stroke is observed in the steppe, forest-steppe and forest zones of the Russian Plain (367,4:100 000; 338,0:100 000 and 282,6:100 000 respectively), simultaneously, these regions account for 57% of all ACE in the RB annually.

The lowest frequency of stroke was observed in the steppe zone of the Trans-Urals, mountain-steppe zone of the Bashkir Urals and trans-Ural forest-steppe zone (214,3:100 000; 252,4:100 000 and 279,5:100 000, respectively), in these natural zones according to annual amount ACE constitute only 43% out of all 6 zones ($\chi^2 < 0,05$).

The frequency of stroke in zones 1, 2 and 3 constitutes 988,0 per 100 000 population, and in zones 4, 5 and 6 – 746,2. By further statistical processing it was stated, that the differences in the stroke frequency reach statistical significance ($p < 0,05$).

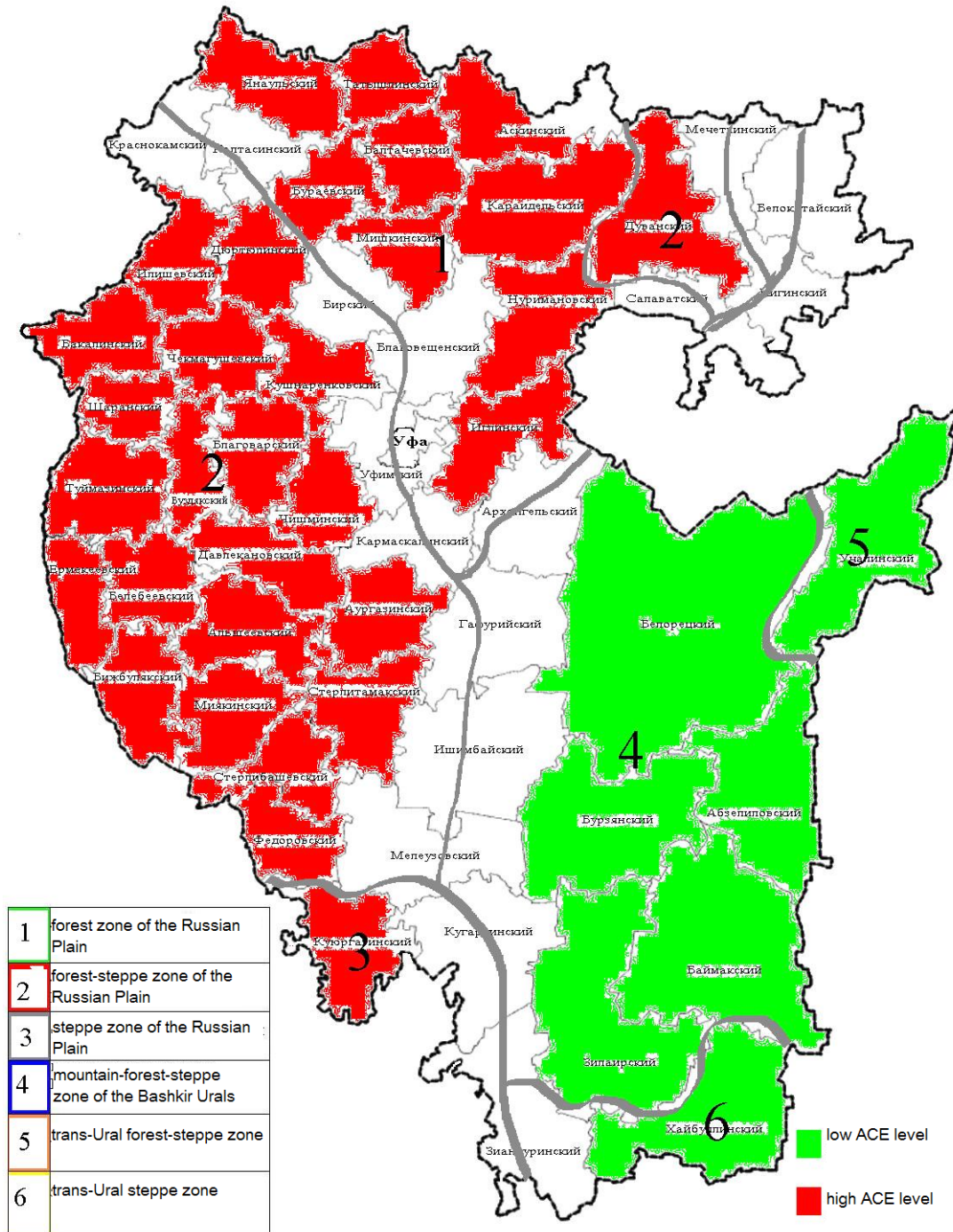


Figure 1. Distribution of RB regions according to natural zones

Conclusion

Consequently, the prevalence of stroke in the RB is not uniform: the relative share of ACE is high in the Northern and Western regions (1, 2 and 3 groups), while the Southern and Eastern territories (4, 5 and 6 groups) are relatively favorable. It is remarkable, that these factors correlate with the indexes of disseminated sclerosis and thyroid disorders prevalence in the RB [1]. The current study once more proves the influence of the microelement content of soil and water both on the whole

organism and the nervous system in particular. In the Southern and Eastern territories of the RB there are spread carbonate rocks, formed in the marine conditions by biogenic and chemogenic type and possessing the optimal microelement content for human organism. On the contrary, the Northern and Western regions of the RB with red bed terrigenous fluvial sediments characterized by non-uniform distribution of microelements are marked by high level of morbidity [1; 3].

Apparently, the frequency of ACE occurrence is influenced not only by natural climatic conditions, but also by social, economic and many other factors. However, during the study process the other effecting factors were neutralized by summation of indexes of administrative regions different by the level of development depending on the reference to a particular natural zone and exclusion of all urban settlements.

It is necessary to create special zonal geographical maps indicating the levels of ACE risk. The research results could be implemented in practice to conduct early stroke prevention.

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ANALYSIS OF THE STRUCTURE AND DYNAMICS OF DISABILITY OF PATIENTS WITH MULTIPLE SCLEROSIS IN THE CITY OF UFA

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A retrospective analysis of the structure and dynamics of disability due to multiple sclerosis in the city of Ufa in the period of 2010-2016 showed that permanent disability is present in 256 (48,5%) patients, 72% of whom are of working age. The majority of persons with disabilities (57%) are characterized by the secondary-progressive course of the disease. There is observed the decrease in the number of persons declared as disabled for the first time, that is most likely connected with the improvement of diagnostics, the advent of multiple sclerosis disease modifying drugs and early start of treatment.

Key words: multiple sclerosis, permanent disability, disability.

Early disability of the working-age population leaves multiple sclerosis (MS) one of the leaders of socially significant diseases, while the main direction of government support is still the pharmaceutical support. Since 2007, in the Russian Federation there has been functioning the program "Seven Costly Nosologies", which provides the patients with drugs changing the course of MS. In many regions there are opened centers or advanced rooms, where, as a rule, work only neurologists conducting diagnostics, supervision of MS patients and selection of immunomodulatory therapy. Nevertheless, in about 10 years since the disease onset about 50% of patients with MS become disabled [1]. By the correct occupational guidance and sustainable job placement and the possibility of rehabilitation in the specialized centers, the majority of working disabled persons could continue labor activity [2]. Due to the absence of existing statistical reporting on the disability (7 social security form) as a separate unit of multiple sclerosis, the exact number of disabled persons due to MS in the Russian Federation is not known. However, exactly the information on the number and structure of MS disability can help the government to pass legal acts for the development of the rehabilitation system and other measures of social support for MS patients and their families.

Objective: to carry out the analysis of the structure and dynamics of disability of patients with MS in the large industrial city of Ufa – the capital of the Republic of Bashkortostan in the period of 2010-2016.

Materials and methods

There was performed the analysis of the information on MS patients for the period of 2010-2016 using the data of the register of patients of the Republican Center of Multiple Sclerosis (RCMS) on the basis of the G.G. Kuvatov Republican clinical hospital (Ufa), examination certificates of disable persons of the Federal State Institution

Central bureau of medical and social assessment in the Republic of Bashkortostan.

For all patients there were filled the questionnaires elaborated by the international working group on studying the epidemiology of MS of the Norwegian Academy of Science and Letters translated and amended by the department of neurology and neurosurgery of RSMU (Gusev Ye.I., Boiko A.N., 1997), which were additionally supplemented by medical and social questions. The obtained results were compared by means of calculating mean values and the error of mean ($M \pm m$). The assessment of intergroup differences by qualitative parameters was performed by means of Pearson's chi-squared test (χ^2) with Yates' correction for continuity using the contingency tables 2x2. The statistical analysis was carried on a personal computer using Statistica 10.0 programs (StatSoft, USA). The critical level of significance by testing of statistical hypothesis in the current research was taken equal to 0,05.

Results and discussion

Totally, in the city of Ufa there reside 527 patients with multiple sclerosis. The prevalence of MS in Ufa as of 1.01.2017 constituted 47,4 per 100 000 population, which allows to refer the region to the zone of the average risk [3]. 256 (48,5%) persons are considered disabled, three of whom are disabled due to other pathology (oncology and diabetes mellitus), 253 – due to multiple sclerosis, upon that, 183 persons (72,3%) are of the working age. The average age of patients with disability - $47,3 \pm 11,6$ (from 15 to 70 years), men - $45,8 \pm 11,4$ (from 22 to 67 years), women - $48 \pm 11,6$ (from 15 to 70 years).

The average age of the occurrence of first disease symptoms in the disable persons constitutes $30 \pm 10,4$, among men - $30,6 \pm 9,8$, in women - $29,7 \pm 10,6$. The earliest occurrence is registered at the age of 5 years in women, the latest – at the age of 58 years in men. The average disease duration in disabled persons with multiple sclerosis consti-

tutes 17,1±9,74 years (in men - 15,1±9, in women - 18,1±9,9). The mean EDSS score in the total cohort of the disabled - 5,3±1 (in men - 5,5±1,3, in women - 5,1±1,3).

During the study period the "Classification and criteria for the medical-social expertise of persons" has been changed for three times, which has led to a considerable reduction of the number of persons firstly considered disabled – from 25 people in 2010 to 15 people in 2016, and in 2016 by the regular survey 2 people were not considered disabled.

We have conducted the comparative analysis of the structure of permanent disability among the persons considered disabled before and after 2010.

In the structure of primary disability, both before 2010 and after prevail the disabled persons of group 3 (84% - in 2010, 60% - in 2016) (Figure 1). However, the share of group 2 in 2016 is higher than in 2010 (33% against 12%). In 2005 in the Republic of Bashkortostan there was carried the epidemiological research, which showed, that the amount of disabled persons with groups 1 and 2 among the patients with MS constitutes 51% [4]. The growth of share of persons with severe disability is probably connected with the imperfection of disability criteria implied nowadays.

In the "Classification and criteria for the medical-social expertise of persons" approved by the decree of the Ministry of labor and social protection of population No. 1024 of 17 December 2015 the preference is given to the degree of paresis intensity

by the examination of patients with multiple sclerosis. Other symptoms of the disease including those, which are not considered focal and are not considered in the EDSS scale (fatigue, pain syndrome, sleep disturbance, sexual dysfunction, emotionally affective disorders), are not taken into account, consequently, the MS patients are not considered disabled by the examination during a long-term period. Moreover, due the program "Seven Costly Nosologies", patients with MS receive MSDMD (multiple sclerosis disease modifying drugs) in full and, in case of working ability, do not apply for disability benefits. Thus, they are forwarded to the Bureau of Medical and Social Assessment with already existing expressed neurologic impairment, and, consequently, are traced to the groups of more severe disability.

The group structure of recurrent disability underwent changes (Figure 2). Among the persons considered disabled before 2010, there prevail disabled persons of group 1 (37%), while in 2016 after re-examination, the general share consisted of patients of group 3 (46%). It can be adequately explained by a wider spectrum of MS therapy and also by the growth of long-term immunosuppressive therapy popularity due to the occurrence of new kinds of medicines with a rarer injection frequency and also due to peroral MSDMD occurrence.

The comparative clinical and epidemiological characteristics of disabled persons is presented in Table 1.

Table 1

Comparative characteristics of MS patients considered disabled in 2010 and 2016

	Primary disability			Recurrent disability		
	2010	2016	p	2010	2016	p
Average age	30,7±9,1	45,6±10,1	0,068	51,2±9,4	43,8±12,3	1,09
Onset age	25,2±8,7	34,8±12,3	0,05*	29,8±9,8	29,6±10,6	0,27
Course						
RMS	12%	6,6%		9,7%	9,5%	
RPT	24%	20%		7,9%	13,5%	
SPMS	64%	53,3%		77%	75,3%	
PPMS		20%		6%	1,5%	
Disease duration	14,2±7,7	10,4±7	0,12	21,4±9,1	14,8±8,8	1,92
Mean EDSS score	5,3±1,25	4,6±0,9	0,04*	5,7±1,4	5,0±1,1	0,0001*
Disease duration before disablement	8,3±7,8	10,4±7	0,49	9,37±7,8	10,3±8,7	0,19

In person primarily considered disable in 2016 the average age was higher than in persons examined before 2010 with the tendency to significance (p=0,068). Also, in 2016, the age of disease onset

(p=0,05) and the degree of disability according to EDSS scale (p=0,04) were higher, which is most likely connected with the improvement of MS diagnostics, availability of MRI and allows to detect

the disease at early stages, to assign the therapy in due course and increase the term of appearance of permanent disability symptoms. The statistical significance in the disease duration and the time from the manifestation of disease to the determination of the disability group was not obtained (* $p=0,12$ and $p=0,49$ respectively).

By the second comparison of the groups of persons recurrently considered disabled before the observation period and in the observation period, there was not registered a statistically significant difference in age, time of appearance of first symptoms, disease duration and time from the manifestation of disease to the determination of the disability group ($p>0,05$), which can be the consequence of insufficient possibilities of rehabilitation organization. The mean EDSS score turned out to be statistically significant by re-examination in the comparison groups ($p<0,001$).

More and more patients with signs of permanent disability have a desire and ability to continue working due to sustainable job placement. During the study period there was registered the increase of the number of working disabled persons from 19,6 % in 2010 to 19 % in 2016 (Figure 3).

In the RF regions, where similar researches took place, the indexes of disability are higher than in Ufa. Thus, in the Amur Oblast, the rate of disabled persons due to multiple sclerosis constitutes 73,2%, in the Kursk Oblast – 60%, in the Tver Oblast – 51%. In the structure of disability there was also marked the prevalence of group 3 [5,6,7].

Conclusion

The average age of disabled persons due to multiple sclerosis in the city of Ufa accounts for the peak of working age and constitutes $47,3\pm 11,6$ years. The imperfection of existing criteria used for the determination of disability by multiple sclerosis “prolongs” the terms of certification of a person as disabled, which leads to a more severe disability. Due to the extensive implementation of MSDMD, appearance of new drug forms, the terms of appearance of permanent disability symptoms has become longer. The growth of rate of patients with multiple sclerosis pertaining working ability can be facilitated by the opening of specialized rehabilitation centers providing psychological help for MS patients and their families. Correct occupational guidance, sustainable job

placement and the availability of surrounding environment for patients with reduced mobility can contribute to the increase of the rate of disabled persons continuing labor activity.

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SYNDROME OF HEMORRHAGIC COLITIS BY ACUTE INTESTINAL INFECTIONS IN CHILDREN: CLINICAL AND LABORATORY CHARACTERISTICS

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There were examined 94 children with acute intestinal infections with developing hemorrhagic colitis. Hemorrhagic colitis syndrome developed primarily in children at the age under 4 years (61%). The main etiological agents of hemorrhagic colitis were salmonella and campylobacteriae (47% in each case), in single cases – Shigella, Yersinia, staphylococcus, Escherichia, Pseudomonas Aureginosa. In all patients with campylobacteriosis and in 34% of patients with salmonellosis, the etiology was determined by detection of causative agent's DNA from the stool, but no by bacteriological examination. In patients with salmonellosis, hemorrhagic colitis developed in later terms since the disease onset and had a harder response to therapy, by campylobacteriosis, on the contrary, it was characterized by earlier development and quicker reduction on the background of therapy. Cefixime, as a drug of etiotropic treatment, showed enough efficiency by campylobacteriosis, while by salmonellosis 22,7% of patients needed the second course of treatment (ceftriaxone).

Key words: acute intestinal infections, hemorrhagic colitis, children.

In the etiological structure of acute intestinal infections in children, the leading position is occupied by virus diarrheas. Nevertheless, bacterial intestinal infections, such as shigellosis, salmonellosis, klebsiellosis, proteose, enterobacteriosis and infections causes by other opportunistic pathogenic agents, still retain their relevance [1, 2, 3].

This is explained by a number of reasons, among which is the severity of the disease course at an early age, possibility of long-term bacterial excretion [4]. The diarrhea syndrome developing by these conditions has an invasive character and can lead to hemorrhagic colitis.

Considering the etiological structure of only bacterial intestinal infections in children, there is commonly observed the reduction of shigellosis share by preserving significance of salmonellosis and potentially opportunistic microorganisms [5, 6]. While the spread of new methods of diagnostics in everyday practice allowed to determine the role of Campylobacter spp. microorganisms as a substantive cause bacterial diarrheas in children affected by hemorrhagic colitis syndrome.

The change of etiological structure of acute intestinal infections (AII) affected by hemorrhagic colitis not only reduced, but also increased the role of its differential diagnostics among the broad range of diseases of both infectious and noninfectious genesis.

The importance of studying clinical, epidemiological and laboratory characteristics of intestinal infections accompanied by hemorrhagic colitis is still present.

Objective: to study clinical and laboratory characteristics of hemorrhagic colitis syndrome developed in children with acute intestinal infections.

Materials and methods

The current research presents the analysis of AII course in 94 children at the age from 1 month to 14 years being hospitalized to the infectious disease department of FSBHI "Municipal hospital №12, Barnaul" in 2016. The inclusion criteria was the development of hemorrhagic colitis.

The study included the following methods:

1. General laboratory tests – general blood analysis, general urine analysis, coprogram.
2. Biochemical tests – serum electrolytes, urine ketones.
3. Bacteriological fecal tests for obligate and opportunistic pathogenic microflora.
4. Polymerase chain reaction for detection of RNA of rotaviruses, noroviruses and astroviruses and DNA of salmonella and campylobacteriae.
5. Microscopic investigation of fecal matter for detection of protozoans.
6. The statistical analysis was performed by means of Biostat 2009 Professional data analysis package.

To estimate the statistical significance of the differences there was used Mann-Whitney U test.

Results and discussion

The age structure of patients in the clinical picture of intestinal infection with developing hemorrhagic colitis is presented in Diagram 1.

According to Diagram 1, the development of hemorrhagic colitis was more often registered in infants and young children (61%) in comparison with the older children.

The number of boys among the examined patients – 48, girls – 46.

The etiological structure of intestinal infections affected by hemorrhagic colitis in the studied children is presented in Diagram 2.

Diagram 1
Age structure of examined patients (%)

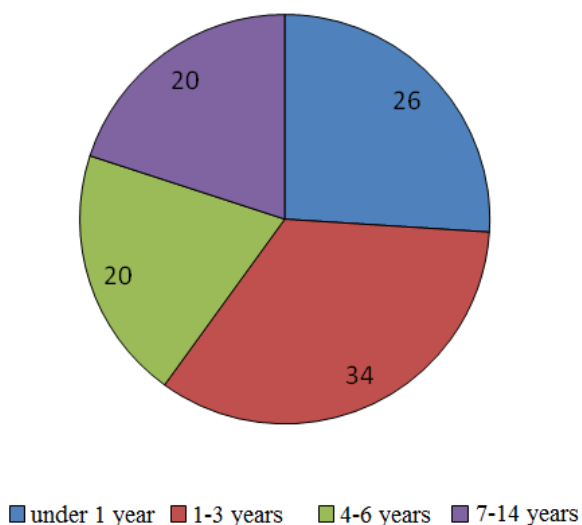
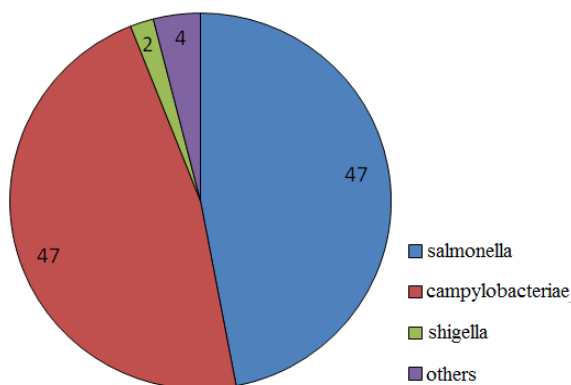


Diagram 2
Etiology of hemorrhagic colitis in examined patients (%)



According to Diagram 2, the main causes of hemorrhagic colitis development in children were salmonella and campylobacteriae (47% of children in each case). Rather rarely the cause of intestinal infection was shigella (only 2%). Among other infection agents causing hemorrhagic colitis in single patients were Yersinia, staphylococcus, Escherichia, Pseudomonas Aureginosa (1% each respectively). In 63% of patients, the local syndrome was presented by enterocolitis, in 37% - gastroenterocolitis.

Taking into account the small number of patients with shigella, Yersinia, staphylococcus, Escherichia and Pseudomonas Aureginosa as a causative agent of hemorrhagic colitis, a more detailed analysis was performed only for salmonellosis and campylobacteriosis.

In all patients with campylobacteriosis and 34% of patients with salmonellosis, the diagnosis was established on the basis of DNA detection from the stool by means of PCR, but not on the basis of conventionally used bacteriological methods of examination.

Salmonellosis proceeding in children with hemorrhagic colitis in 48% of patients was associated with rotavirus. By campylobacteriosis hemorrhagic colitis, such association was registered not more than in 16% of cases.

On the basis of concomitant pathology, there was noticed high frequency of anemia development – 41%, moreover, on the background of campylobacteriosis, it developed 1,6 times oftener than by salmonellosis *25% and 16% respectively, the difference is statistically significant, $P(0,001)$.

Nearly three quarters of children (74,5%) were admitted to hospital during first three days of the disease. The average term of disease duration for the moment of admission constituted $3,2 \pm 0,3$ days. In all children intestinal infection proceeded in moderate form.

Hemorrhagic colitis manifestations by the moment of hospital admission were registered in 42 children (44,7%), while by campylobacteriosis it took place in 64% of children, by salmonellosis – only in 29,5% of children. It would be interesting to analyze the terms of hemorrhagic colitis development according to the days of illness, which is presented in Diagram 3.

The data of Diagram 3 demonstrate, that intensive formation of hemorrhagic colitis in patients with campylobacteriosis occurred on the 2nd-3rd day of illness, by the 4th day this syndrome was present already in 73% of patients. By salmonellosis the occurrence of hemorrhagic colitis syndrome was observed in later terms, primarily after the 5th day of illness.

Manifestations of hemorrhagic colitis had a moderately expressed character and were characterized by the presence of mucus and blood streaks in the fecal matter. Coprological examination revealed the presence of mucus, erythrocytes and increased concentration of leucocytes in all children.

The intensity of diarrhea syndrome at the ambulatory stage (frequency of defecation per day) by campylobacteriosis constituted $9,6 \pm 0,7$, by salmonellosis - $7,3 \pm 0,7$ (the difference is statistically significant, $P < 0,001$). On the contrary, during the hospital treatment its manifestations were opposite: diarrhea syndrome was more intensive by salmonellosis - $12,7 \pm 1,1$ defecation events, against $9,3 \pm 0,7$ events by campylobacteriosis.

The duration of hemorrhagic colitis at the hospital stage of treatment constituted averagely $2,4 \pm 0,1$ days. In spite of the similar duration of hemorrhagic colitis in patients with salmonellosis and campylobacteriosis, the dynamics of its reduction on the background of the conducted antibacterial therapy turned out to be different, which is presented in Diagram 4. Hemorrhagic colitis was reduced slower in patients with salmonellosis than in patients with campylobacteriosis. The data of Diagram 4 show, that already in 3 days after the conducted antibacterial therapy, by campylobacteriosis

it retained only 20% of patients, while by salmonellosis – in 50%, in 4 days – 7% and 27% respectively (the difference during these days is statistically significant, $P < 0,001$).

The total duration of diarrhea syndrome constituted $5,7 \pm 0,4$ days by salmonellosis and $4,2 \pm 0,3$ days by campilobacteriosis (the difference is statistically significant, $P < 0,001$).

Diagram 3

Terms of hemorrhagic colitis development according to etiology

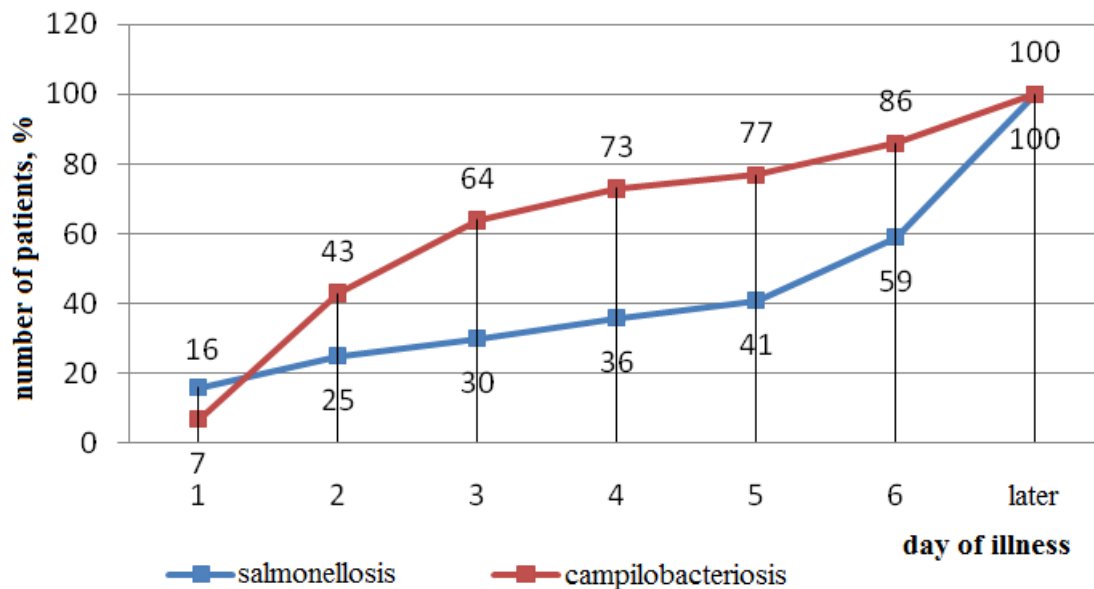
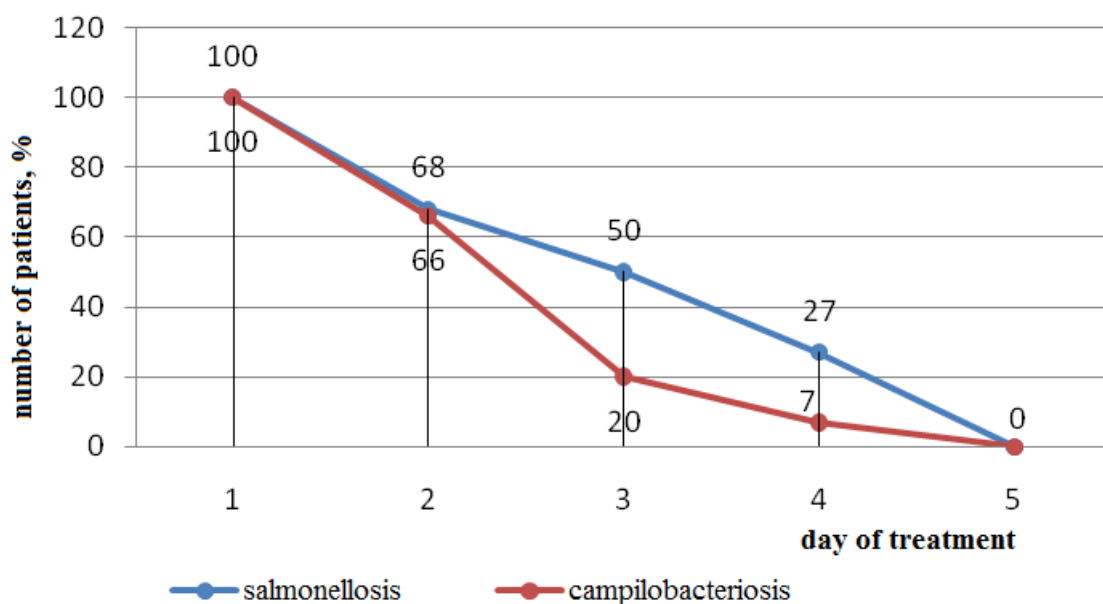


Diagram 4

Reduction of hemorrhagic colitis in relation to the duration of antibacterial treatment



The general infectious syndrome was manifested in patients in the temperature rise, loss of appetite, reduction of physical activity, disturbance of sleep. The temperature rise was registered practically in all patients (94,7%). Its degree constituted $38,7 \pm 0,1^{\circ}\text{C}$ irrespective of the etiology of the intestinal infection. The duration of temperature response in patients with salmonellosis constituted $4,4 \pm 0,3$ days, while by campilobacteriosis - $3,7 \pm 0,2$ days (the difference is statistically significant, $P < 0,001$).

The general blood analysis at the acute stage of the disease in patients with salmonellosis showed leukocytosis in 61,4% patients, neutrocytosis – 54,5%, ESR boost – 20,4%, by campilobacteriosis the same indexes were registered with a different frequency: 34,1% - 38,8% - 9,0% respectively (the difference is statistically significant for all indexes, $P < 0,001$).

The etiotropic treatment in children included cefixime as a starting drug, moreover, by campilobacteriosis treatment the change of antibiotic

treatment and administration of the second course of etiotropic therapy (ceftriaxone) was required only in 9% of patients, while by salmonellosis the same changes took place in 22,7% of cases (the difference is statistically significant, $P < 0,001$).

The pathogenic therapy included oral, enteral (diosmectit octahedral) and infusion detoxication. According to the indications, the patients received enzymes (creon), probiotics (saccharomyces boulardii).

The average bed day by campilobacteriosis constituted $5,5 \pm 0,2$ days, by salmonellosis - $7,2 \pm 0,5$ days.

Conclusion

1. The main etiological factors of intestinal infections affected by hemorrhagic colitis syndrome in children at the current stage are salmonella and campylobacteria.

2. The hemorrhagic colitis syndrome develops primarily in children at the age under 4 years, the rational antibacterial therapy allows to reduce it not later than the 4th day of treatment.

3. In patients with salmonellosis, hemorrhagic colitis developed at later stages since the disease onset and had a harder response to therapy, by campilobacteriosis, on the contrary, it was characterized by earlier development and quicker reduction on the background of therapy.

4. Parallel use of bacteriological examination and methods of agent's DNA detection allows to improve the etiological diagnostics of intestinal infections.

5. Cefixime, which had shown high efficiency, is recommended as an etiotropic means by treatment of acute intestinal infections in children affected by hemorrhagic colitis.

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THE ALGORITHM OF LABORATORY TESTS TO PREDICT CEREBRAL LESIONS BY PERINATAL HYPOXIA

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In a randomized prospective clinical study involving 150 women and newborns there are evaluated the operational characteristics of the umbilical cord blood tests in relation to the differential diagnosis of perinatal hypoxic cerebral lesions in newborns. The method of multidimensional scaling revealed that the algorithm based on the combination of the levels of matrix metalloproteinase-9 (MMP-9), thiobarbiturate-reactive substances (TBARS), erythropoietin and lactate in the first hours after birth allows to predict perinatal hypoxic cerebral lesions with a sensitivity of 85% and a specificity of 90%.

Key words: perinatal hypoxia, laboratory biomarkers.

Perinatal hypoxia (PX) is a pathological state of the perinatal period developing due to the lack of oxygen delivery to the organism of the fetus and/or its uptake during pregnancy (chronic intrauterine hypoxia), delivery (acute fetal hypoxia, asphyxia), early neonatal period [1, 2]. PX complication is the multiple organ damage in the fetus and newborn which manifests itself through various nosological forms [3]. Herewith, 15-20% of all PX complications both in mature and premature newborns constitute hypoxic-ischemic encephalopathy and intraventricular hemorrhage. These central nervous system (CNS) damages by PX are revealed according to neurological symptoms and the data of ultrasound investigation, as a rule, not earlier than on the 3rd-4th day of age [4-6].

Diverseness and remoteness of the manifestation of clinical and neurovisualization symptoms of PX complications from the moment of birth considerably complicate timely diagnosis and, consequently, the effectiveness of prevention and correction of target organ lesions, including CNS damages [7, 8]. This stimulates the search of biochemical markers for the prognosis and early diagnosis of perinatal hypoxic damages [9, 10].

It is known, that the key stages of PX pathogenesis are such metabolism disorders induced by hypoxia-reperfusion and interrelated systemic disorders as the increase of lactic-acid fermentation, free-radical oxidation, increase of matrix metalloproteinases activity [11-14]. As the compensatory reaction by PX is considered the growth of erythropoietin production [15, 16].

In this regard, **the research objective** was to elaborate the algorithm of prognosis of CNS damages in newborns by PX on the basis of complex of pathogenetic laboratory indexes of systemic metabolic disorders.

Materials and methods

The randomized prospective clinical study included 150 pregnant women and their newborns

separated into two groups depending on the presence/lack of symptoms of perinatal hypoxic CNS lesions in newborns at the early neonatal period.

The exclusion criteria were: immunoincompatible and multifetal pregnancy; delivery time less than 28 weeks; presence of reproductive disorders in the medical history of a woman, extragenital diseases at the stage of subcompensation and decompensation, preeclampsia; drug and/or toxic (including alcohol) dependence, diabetes mellitus; presence of congenital abnormalities and genetic metabolic disorders in the newborns.

The formed groups of mothers of the newborns did not differ in the age, social status, obstetric and gynecological anamnesis, presence of chronic extragenital diseases. The clinical characteristics of the newborns is presented in Table 1.

PX was diagnosed on the basis of presence of not less than two following symptoms: intranatal distress with fetal bradycardia, 100 and more beat per minute according to cardiotocography; 6 and less points according to the Apgar scale on the 5th minute; requirement of resuscitation for more than 1 minute [4]. CNS lesions were evaluated on the basis of symptoms of hypoxic-ischemic changes in the brain according to the data of ultrasound investigation on the 3rd-4th day of birth. Newborns with PX were transferred to the department of intensive therapy, where there were conducted essential resuscitation procedures including artificial lung ventilation (ALV).

In the newborns there was performed the standard laboratory examination (general blood analysis, differential leucocyte count, the level of bilirubin, urea, creatinine, crude protein, aminotransferase, alkaline phosphatase, glucose, lactate, potassium, sodium), screening examination for phenylketonuria, cystic fibrosis, hypothyroidism, adrenogenital syndrome and galactosemia. For the specific tests immediately after the birth there was taken venous blood from the umbilical artery into vacutainers with lithium heparinate (14 UN per

Table 1

Clinical characteristics of the newborns

Index	Newborns without perinatal hypoxic CNS damage n = 62	Newborns with perinatal hypoxic CNS damage n = 40	Significance of differences, p
Delivery term	39,3 ± 4,95	34,8 ± 3,1	< 0,001
Weight (kg)	3379,0 ± 461,38	2415,5 ± 892,97	< 0,001
Apgar 1st min	7,2 ± 0,82	6,000 ± 0,96	< 0,001
Apgar 5th min	8,1 ± 0,68	7,1 ± 0,55	< 0,001
ALV, n (%)	5 (8,1)	24 (60)	< 0,001
ALV - mask, n (%)	0 (0)	3 (7,5)	< 0,001
Respiratory distress-syndrome, n (%)	4 (6,4)	30 (75)	< 0,001
Caesarean operation, n (%)	28 (90,3)	23 (88,5)	0,974
Amniotomy, n (%)	2 (6,5)	2 (7,7)	0,974
Syndrome of CNS damage:			
Distress, n (%)	3 (4,8)	34 (85)	< 0,001
Activation, n (%)	1 (1,6)	2 (5)	< 0,001
Type of CNS damage:			
Hypoxice, n (%)	0 (0)	8 (20)	< 0,001
Ischemic-hypoxic, n (%)	4 (6,4)	28 (70)	< 0,001

Note: quantitative variables are presented in the form of M (arithmetic mean) ± SD (standard deviation).

1 ml blood), and also into vacutainers with sodium fluoride and K₂-EDTA (3,3 and 1,2 mg per 1 ml blood respectively).

In the blood serum by means of the enzyme immunoassay there was measured the concentration of matrix metalloproteinases (MMP-1, MMP-2, MMP-9), tissue inhibitor of matrix metalloproteinases (TIMP-1) using test systems produced by "RayBiotech" (USA); erythropoietin, S100B protein using test systems produced by "Biomerica" (USA) and "CanAG" (Sweden) respectively; by means of absorption photometry there was measured the concentration of lactate with reagents "Biocon" (FRG) and products of lipid peroxidation of thiobarbiturate-reactive products (TBRP) with reagents "ZeptoMetrixCorporation" (USA).

The study is approved by the Ethics Committee of the FSBEI HE Altai State Medical University of the Ministry of Health of the Russian Federation, performed on the clinical base of RSBHI Altai Krai Perinatal (clinical) center (Barnaul) in the period from 2008 to 2012.

By the statistical analysis of the study results by means of SigmaPlot 11.0 program there was evaluated the normality of distribution of variables according to Shapiro-Wilk test, intergroup differences of quantitative variables according to Mann-Whitney U test, categorical variables according to chi-square. Mathematical modelling by means of multidimensional scaling, visualization of the diagnosis algorithm and associated calculations were performed by means of JMP 7.0 program (SAS Institute, USA) in the mode Partition, ROC-analysis (receiver operating characteristic analysis) – in MedCalc 9.1.0.1 program. The critical level for all used criteria was considered $p < 0,05$.

Results and discussion

According to the analysis, the ROC-curve distribution of the values of all studied parameters, except for TIMP-1 concentration, and also the calculated rates (relation of the level of stated matrix metalloproteinases to the level of TIMP-1) differed significantly from the distribution with the area 0,5 (Table 2). This indicates the possibility of using these indexes as biomarkers to prognosticate CNS disorders by PX. The biggest area under ROC-curve is determined for erythropoietin, TBRP, lactate, MMP-2 and relation MMP-2/TIMP-1.

Table 3 presents operational characteristics of the studied parameters. According to the data, the combination of high sensitivity and high specificity in terms of CNS lesions in the newborns with PX rational for clinical practice was not revealed for any of the examined indexes. Consequently, it is logical to search for the combination of tests with high sensitivity and tests with high specificity.

In order to solve the stated problem, there was carried mathematical modelling of the laboratory algorithm of prognosis of cerebral disorders in the newborns by perinatal hypoxia. In terms of modelling there was stated that, according to the rate of true-positive and true-negative results, the best result of differentiating the newborns according to the studied pathology is achieved by using the levels of TBRP, lactate, MMP-9 and erythropoietin. The quantitative evaluation of the combination of these tests showed, that sequential analysis of the levels of MMP-9, TBRP, lactate and erythropoietin (Fig.) allows to reveal 85,0% of newborns with perinatal hypoxic CNS lesion (sensitivity 85%) and 90,0% of newborns without such pathology (specificity 90%) already in the first hours of birth.

Table 2

Area under ROC-curve for tests in the venous blood plasm from the umbilical artery of the newborns in relation to the prognosis of cerebral damages by perinatal hypoxia

Test	n	Area under ROC-curve (CI _{95%})	p
Erythropoietin	56/85	0,807 (0,732–0,869)	<0,0001
TBRP	57/87	0,807 (0,733–0,868)	<0,0001
Lactate	55/85	0,782 (0,705–0,848)	<0,0001
MMP-2	55/84	0,699 (0,616–0,774)	<0,0001
MMP-2/TIMP-1	51/79	0,679 (0,591–0,758)	0,0007
MMP-1	58/85	0,672 (0,589–0,748) ^{ab}	0,0004
MMP-1/TIMP-1	53/78	0,667 (0,580–0,747) ^{abc}	0,0005
MMP-9	54/84	0,646 (0,560–0,726) ^{abc}	0,0099
S100B protein	59/84	0,610 (0,525–0,690) ^{abc}	0,0304
MMP-9/TIMP-1	50/81	0,610 (0,521–0,694) ^{abc}	0,0368
TIMP-1	54/85	0,527 (0,440–0,612) ^{abc}	0,5903

Note: CI_{95%} – 95% confidence interval; n – number of newborns with cerebral lesion by perinatal hypoxia/number of newborns without lesions; p – significance of difference of the area under ROC-curve in comparison with 0,5; abc – p<0,05 for the area under ROC-curve in relation to the same value for TBRP, erythropoietin and lactate respectively.

Table 3

Operational characteristics of tests in the venous blood plasm from the umbilical artery of the newborns in relation to the prognosis of cerebral damages by perinatal hypoxia

Test	Border	Sp (CI _{95%})	S (CI _{95%})	+LR/-LR	+PV/-PV
Erythropoietin, mUn/ml	>56,2	57,1 (43,2–70,3)	91,8 (83,8–96,6)	6,94/0,47	82,1/76,5
TBRP, mmol/l	>31,9	75,4 (62,2–85,9)	79,3 (69,3–87,3)	3,65/0,31	70,5/83,1
Lactate, mmol/l	>8,5	63,6 (49,6–76,2)	82,4 (72,6–89,8)	3,61/0,44	70,0/77,8
MMP-2, ng/ml	≤49,2	47,3 (33,7–61,2)	95,2 (88,3–98,7)	9,93/0,55	86,7/73,4
MMP-2/ TIMP-1	≤1,98	51,0 (36,6–65,2)	86,1 (76,5–92,8)	3,66/0,57	70,3/73,1
MMP-1, ng/ml	>305,7	62,1 (48,4–74,5)	71,8 (61,0–81,0)	2,20/0,53	60,0/73,5
MMP-1/ TIMP-1	≤0,014	71,7 (57,7–83,2)	57,7 (46,0–68,8)	1,69/0,49	53,5/75,0
MMP-9, ng/ml	>107,1	50,0 (36,1–63,9)	95,2 (88,3–98,7)	10,50/0,53	87,1/74,8
Protein, S100B, ng/l	>0,99	45,8 (32,7–59,2)	79,8 (69,6–87,7)	2,26/0,68	61,4/67,7
MMP-9/ TIMP-1	>4,16	44,0 (30,0–58,7)	82,7 (72,7–90,2)	2,55/0,68	61,1/70,5
TIMP-1, ng/ml	>21,9	81,5 (68,6–90,7)	34,1 (24,2–45,2)	1,24/0,54	44,0/74,4

Note: Sp – specificity; S – sensitivity; +LR – positive relation of chances; -LR – negative relation of chances; +PV – accuracy of determination of positive results; -PV – accuracy of determination of negative results.

It should be noted, that by modelling the algorithm on the basis of maximum coefficient of separation into the groups “disease – no disease” somehow change the borders of tests included into the algorithm in relation to the borders stated by ROC-analysis (Fig. 1 and Table 3). This, in its turn, causes the change of sensitivity and specificity of tests and also the creation of cycles – backup to the tests of the previous level by certain results. At the same time, the cyclic character of the algorithm does not require any additional laboratory investigations, and only complicates a little the interpretation of the results at the postanalytical phase.

It appears that the elaborated algorithm of prognosis of hypoxic cerebral damages in the newborns based on four tests in the plasm of umbilical blood is promising for the validation in prospective studies. In terms of practical implementation of the al-

gorithm rational is the elaboration of express methods of measuring MMP-9 and erythropoietin levels and computer program for result analysis.

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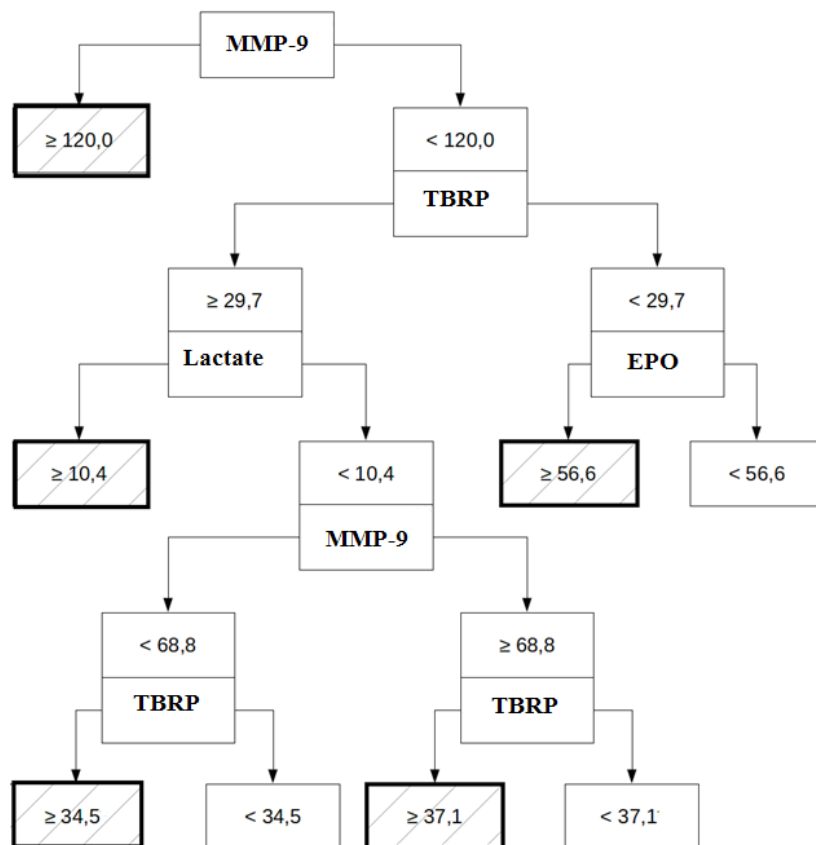


Figure 1.

Algorithm of differential diagnosis of perinatal hypoxic CNS damage in the newborns based on laboratory tests in the umbilical blood Units of concentration like in Table 3; hatching shows the borders identifying the newborns with perinatal hypoxic CNS damage

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MODERN APPROACHES TO SURGICAL TREATMENT OF PANCREATIC NECROSIS

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A retrospective analysis of surgical treatment of 581 patients with pancreatic necrosis with its delimited and widespread forms was conducted. It was found that with abscessed (delimited) forms of purulent process, lethality was 9,1% (10 patients), whereas in generalized, purulent-septic phlegmon of retroperitoneal tissue it reached 50,2% (101 deaths). Experimental studies have shown that in the process of limitation, the leading role is played by the restoration of perfusion blood circulation deficiency in the zone of ischemic pancreatic tissue with the help of local rheological therapy (alprostadil). Along with this, it is established that the processes of restriction in retroperitoneal cellulose are affected by the immaturity of fibrin, which is constantly destroyed by enzymes of the pancreas. In this connection, the possibility of creating a tissue barrier on the path of enzymatic impregnation with the help of a fibrinogen donor (cryoprecipitate) is shown. Achieving early delimitation of the enzymatic-inflammatory process in retropancreatic cellulose allows the formation of cysts or fluid clusters, which can be drained with the help of minimally invasive technologies.

Key words: pancreatic necrosis, pancreatic cysts, rheological therapy, delimitation barrier, minimally invasive technologies.

In recent years, the problem of pancreatic necrosis (PN) has been the leading one in urgent surgery [1]. It is connected with high incidence, which today constitutes from 200 to 800 cases per 100 thousand people [2]. According to professor A.V. Shabunin, in 2015 – 2016 acute pancreatitis took the lead in urgent pathology in Moscow. In other regions it holds stable second or third positions according to incidence. Acute pancreatitis case mortality rate ranges between 18–20%, while by infected forms of pancreatic necrosis it reaches 30% [3,4,5]. If the diagnostics of acute pancreatitis is characterized by a significant progress [6], the surgical tactics involves a variety of methods and approaches far from standard decisions [7,8,9]. In this regard, the problem of delimitation of enzymatic process and inflammatory process, which to a great extent determines progressive course of illness, is of special interest [10]. The elaboration of stimulation methods of delimitation processes and rational surgical approaches is expedient at modern stage, the terms of surgery and choice of method depend exactly on them. The arsenal of surgeons includes both minimally invasive technologies [11, 12, 13, 14] and open methods of treatment, which have their own pathogenetic ground in a number of patients [15].

Objective: to study the possibilities of delimitation of enzymatic-inflammatory process in pancreatic gland and retroperitoneal cellulose in patients with pancreatic necrosis.

Materials and methods

In 2014 in a clinical setting, there were conducted researches devoted to the evaluation of blood circulation in the tissue of pancreatic gland (PG) by pancreatic necrosis [16]. By angiography of celiac

artery, circulation there was revealed the blockage of distal blood stream, determined by the disorder of microcirculation and edema of pancreatic gland tissue. The main angiographic feature by the insertion of catheter into gastroduodenal artery (GDA) was the depletion of blood stream of head, body and tail of pancreatic gland (Figure 1).

Exactly the disorders of blood circulation in PG stipulate further necroses, enzymic fistulas with the extension of inflammatory process on retroperitoneal cellulose. Thus, the intake of drugs improving blood circulation in pancreatic gland at early stages seems appropriate. However, their systemic implementation preconditions the risk of bleedings. At the same time, clinical practice possesses the experience of using topical drugs improving regional blood flow. In this context, there was conducted comparative examination of 125 patients with acute pancreatitis divided into 3 groups. Traditional technologies in patients with open surgeries (1 group) by pancreatic necrosis were compared to patients with local regional therapy in gastroduodenal artery and celiac artery (Table 1).

In the second group of patients there was used alprostadil (vazaprostan) aimed at the liquidation of endothelial dysfunction and opening of peripheral blood stream. The drug is intended for intra-arterial injection. Finally, in patients of the third group there was made intra-arterial injection of pentoxifylline with heparin aimed also at anti-aggregatory activity and opening of blood stream. The groups were comparable according to gender, age, duration of disease and also main laboratory parameters (Table 1). The inflammatory process by acute pancreatitis in all groups was characterized by high leukocytosis, stab shift with the increase of enzyme activity.

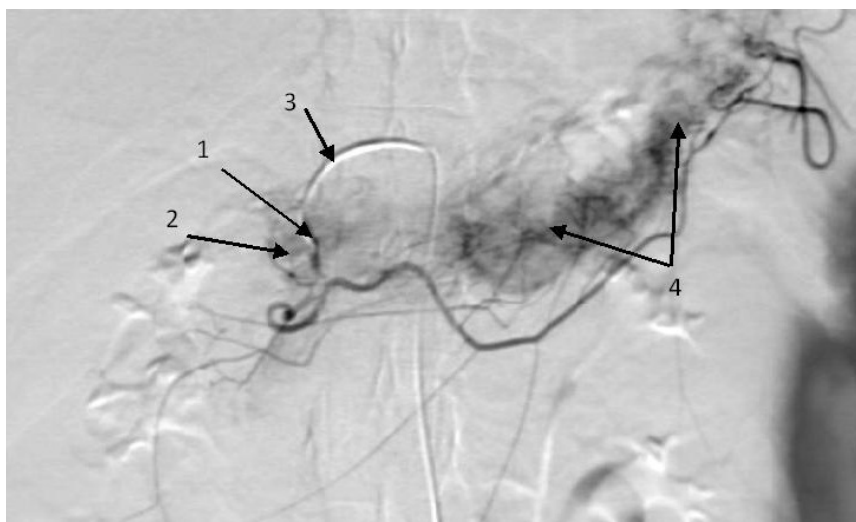


Figure 1.
Angiography in GDA: 1 – GDA; 2 – depletion of blood stream in the zone of head;
3 – catheter in GDA; 4 – deposition of contrast in body and tail of pancreatic gland

Table 1

Initial main laboratory parameters in patients with acute pancreatitis in groups

Parameter	Control	Group 1 (n=27)	Group 2 (n=33)	Group 3 (n=65)
		X±m	X±m	X±m
Hemoglobin gm/dl	120,3±1,3	120,6±4,7 p1-2>0,05	127,6±4,7 p2-3>0,05	124,0±4,5 p1-3>0,05
Thrombocytes x10 ⁹	280,7±15,7	288,9±14,5 p1-2>0,05	303,9±25,9 p2-3>0,05	292,3±17,4 p1-3>0,05
Leucocytes x10 ⁹	8,3±1,6	14,9±0,7*** p1-2>0,05	15,2±0,8*** p2-3>0,05	14,5±0,4*** p1-3>0,05
Stab neutrophiles	2,1±1,7	13,6±1,1*** p1-2>0,05	16,4±1,6*** p2-3>0,05	14,4±0,9*** p1-3>0,05
Creatinin mcmol/l	115,8±11,8	126,8±10,0 p1-2>0,05	123,8±13,0 p2-3>0,05	130,2±10,8 p1-3>0,05
Urea mcmol/l	8,5±0,7	9,6±1,1 p1-2>0,05	9,7±0,9 p2-3>0,05	9,6±0,9 p1-3>0,05
Total protein gm/dl	74,5±2,1	60,0±1,6*** p1-2>0,05	64,4±1,2*** p2-3>0,05	60,6±1,1*** p1-3>0,05
Amylase u/l	67,3±9,5	223,1±30,2*** p1-2>0,05	480,6±87,3*** p2-3>0,05	256,0±31,9*** p1-3>0,05
Total bilirubin mmol/l	16,5±1,4	23,5±2,6* p1-2>0,05	32,8±5,7** p2-3>0,05	28,0±2,9*** p1-3>0,05

Note: statistically significant differences of control with parameters of 1,2 and 3 groups: * – p<0,05, ** – p<0,01, *** – p<0,001.

As a result, it was determined, that the implementation of local rheological therapy at early stages allows to abort the inflammatory process in pancreatic gland. Patients show the decrease or liquidation of infiltrates, drop in the number of lavages of the abdominal cavity from 3 to 1, shortage of the number of in-patient days from 35,8 to 24,8. The second and third groups of patients show the decrease of mortality (Table 2).

The conducted control angiography of GDA circulation showed, that intra-arterial injection of alprostadil into arterial phase leads to the resto-

ration of arterial stream in the head with decrease into the venous phase of the stasis of contrast agent in the head and tail of the pancreatic gland (Figure 2).

Especially effective was alprostadil (vazaprostan) by injection into gastroduodenal artery. Intra-arterial drug injection determined the pain management, contributed to the prevention of necrosis site formation in the head of pancreatic gland or decrease of their depth (Fig. 3A, B). This effect is important in the prevention of small passages and the flux of enzymes into cellulose.

Results of surgical treatment in groups of patients with pancreatic necrosis

Parameters	1 group M±m	2 group M±m	3 group M±m
Number of patients (n)	71	23	12
APACHE – 2 (grades)	12,3±0,7	12,7±1,1	11,8±2,9
Number of abdominal cavity lavages	3,1±0,3	1,0±0,3	1,0±0,5
	P ₁₋₂ <0,001	P ₁₋₃ <0,001	P ₂₋₃ >0,05
Inpatient day	35,8±2,3	24,8±3,6	23,6±2,1
	P ₁₋₂ <0,05	P ₁₋₃ <0,05	P ₂₋₃ >0,05
Mortality (%)	16,9	0	0

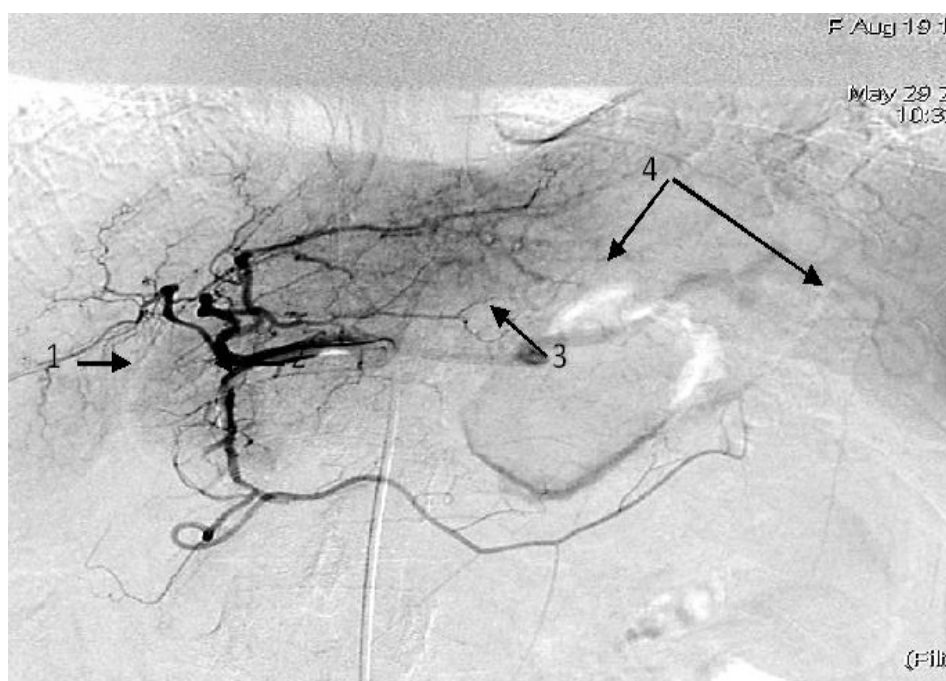


Figure 2.

Angiography in GDA after intra-arterial injection of alprostadil: 1 – appearance of vascular pattern in the head of PG; 2 – catheter in the gastroduodenal artery; 3 – appearance of splenic artery; 4 – lack of deposition in the body and tail of pancreatic gland

The implementation of disaggregant infusion in combination with antibacterial therapy at late stages preconditions a less expressed clinical effect, but improves the results of treatment due to preservation of abacterial environment in the tissues of pancreatic gland not influencing the course of inflammation in the retroperitoneal cellulose.

A considerable number of clinical and experimental researches are devoted to the extension of inflammatory process to the retropancreatic cellulose by pancreatic necrosis. In the work of Fedina I.V. [17] it was for the first time shown, that the pancreatic capsule in its back surface is significantly thinner than its front and includes only one layer of connective tissue cells. The retroperitoneal surface of the capsule has the areas of entry of vessels, through which the enzymic effusion enters cellulose and preconditions the progress of toxemia. According to our previous research

[18], retroperitoneal space produces direct resorption of enzymic effusion into the systemic blood circulation. The matter is that the liver with its reticulo-endothelial system is an effective barrier on the way of toxin influx into the systemic blood stream. The adjunction of their resorption from retroperitoneal cellulose boosts toxemia due to influx of toxic product through lumbar veins into lower hollow vein and further into lungs forming lung injury – lung distress syndrome.

This serve the basis for the analysis of treatment results of 581 patients with pancreatic necrosis with its delimited and common forms. Delimited forms included abscesses of pancreatic gland and retroperitoneal cellulose having capsule in 118 patients. Common forms classified as phlegmons of retroperitoneal cellulose or, according to the current classification, sterile or infected retroperitoneal necrosis, were registered in 200 patients. The others

had sterile pancreatic necrosis. The consisted of 406 men (69,8%), 175 women (30,2%). The average age was 47 ± 68 years. The analysis of surgical treatment showed, that the mortality in patients with PN constituted 19,8% (114 cases). Mortality by sterile type was low – 3 patients (0,8%), which is connected with the lack of purulo-necrotic inflammation. By the infected forms of PN (abscess, phlegmon) the frequency of lethal outcomes grew and reached 32,7% (111 patients). It is characteristic that the rate of mortality in this group turned out to be signifi-

cantly differentiated. Thus, by abscess (delimited) forms of purulent process it constituted 9,1% (10 patients), while by generalized purulent-septic phlegmons of retroperitoneal cellulose it grew up to 50,2% 9 (101 case). Consequently, even by infected PN in case of formation of good tissue delimitation (demarcation zone) there is the possibility to localize the infection in the necrosis areas (abscessation or cyst formation). This aspect is a relatively favorable outcome and significantly improves the chances of recovery.

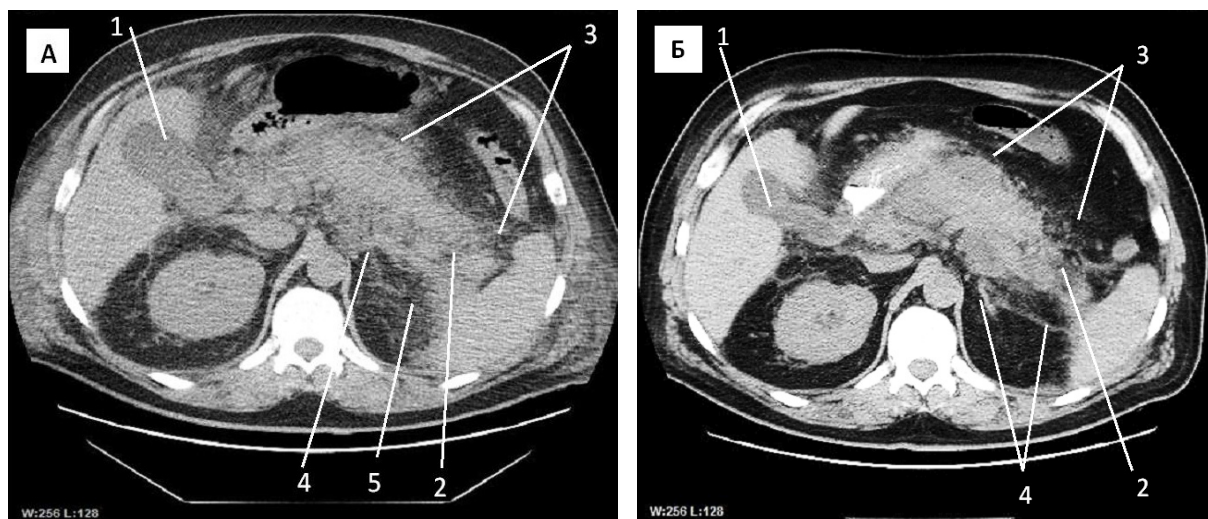


Figure 3. Computer tomography

A – Pancreatic necrosis. 3rd day of the disease before intra-arterial injection of alprostadil: 1 – enlargement of gall bladder; 2 – tissue necrosis in the zone of PG tail, 3 – edema and infiltration in the parapancreatic cellulose in the zone of body and tail of PG, 4 – edema and infiltration of retropancreatic cellulose, 5 – edema and infiltration of the front folium of the left pararenal fascia. B – Pancreatic necrosis after the treatment on the 5th day (the same patient): 1 – decrease of gall bladder size; 2 – necrosis in the zone of PG tail; 3 – decrease of edema and infiltrative changes in the parapancreatic cellulose in the zone of body and tail of PG, 4 – decrease of edema and infiltration of retropancreatic cellulose and the front folium of the left pararenal fascia

In confirmation of that, we had conducted a series of experiment modelling the correlation of plasm fibrinogen/fibrin with proteolytic enzymes (chymopsin) really occurring by pancreatic necrosis in parapancreatic infiltrate. For this purpose were used: native stabilized human plasm and officinal diagnostic and treatment agent – 5% solution of aminocaproic acid (OAO “Krasfarma”, Krasnoyarsk, RF), thrombin (OOO “Technology-Standard”, Barnaul, RF), 1% solution of calcium gluconate (OAO “Farmak”, Kiev, Ukraine), solution of chymopsin (OOO “Samson”, Saint-Petersburg, Russia). The conducted tube tests showed, that the enzymes of pancreatic gland (fresh native juice, Chymopsin drug) possess the expressed properties for the suppression (rapid slowdown) of fibrin clot formation in human plasm. However, the most interest was attracted by a series of experiments aimed at the study of dynamics of unstable fibrin clot lysis under the influence of both native juice of pancreatic gland and the standardized drug Chymopsin (chymotrypsin + trypsin). To make the process maximum objective there was evaluat-

ed the dynamics of the weight change of the newly formed fibrin clots in the context of 60 second (1 group) and 900 second (2 group) maturity.

As it is shown in Table 3, the addition of chymopsin into the tubes with fresh fibrin clots in the first series of experiment lead a significant and statistically valid lysis of freshly obtained fibrin clots, mainly up to 2/3 of the initial weight. It is typical, that proteolytic enzymes did not influence the weight of more mature clots (900 second maturity), in other words, did not lead to their lysis (Table 3).

Consequently, the intensive process of fibrin formation in the retroperitoneal cellulose by acute pancreatitis can be simultaneously and continuously accompanied by proteolytic lysis of newly formed unstable (immature) fibrin (fibrinolysis) by the enzymes of pancreatic gland actively entering the retroperitoneal cellulose.

Thus, the lack of biologically consistent delimiting tissue barrier by infected pancreatic necrosis is extremely unfavorable for the course of illness with uncontrolled extension of septic phlegmon in

the retroperitoneal cellulose and influences badly the prognosis of pancreatic necrosis course.

The analysis of immediate clinical outcomes of the surgical treatment of patients with pancreatic necrosis and experiments showed the necessity of conduction of treatment measures aimed at the localization of purulent-destructive process and constraint of the spread infection in the form of local center – cyst or abscess. This condition could be reached by means of formation of an effective natural or artificial tissue delimitation barrier, while the process is localized in the borders of parapancreatic cellulose and its course is aseptically. According to this assumption, there were conducted experiments on 8 animals (outbred dogs weighing from 20 to 28 kg) with modelling of acute pancreatitis and further creation of an artificial fibrin barrier in the retroperitoneal cellulose.

The natural donor of fibrinogen was the blood product - cryoprecipitate, made out of fresh-frozen donor cryoplasm. The original experimental method of creation of fibrin "tissue barrier" included injected infiltration of parapancreatic cellulose by cryoprecipitate solution in combination with solutions of aminocaproic acid and calcium gluconate. To obtain the medical parapancreatic infiltrate the retroperitoneal parapancreatic cellulose was injected with 50-75 ml of such mixture on the model of experimental pancreatic necrosis. The analysis of histologic specimen revealed, that parapancreatic fatty tissue, already on the 1st day after the experiment, contained a network of numerous small centers (deposits) of fibrin. Especially well observed were numerous insular deposits of "fresh" fibrin on the background of leukocytic infiltration in the retroperitoneal cellulose.

Table 3

The dynamics of dissolution of freshly formed fibrin clots by their reaction with chymopsin drug (5 mg) and 5% aminocaproic acid (daily exposure dose)

Laboratory experiment conditions	Fibrin weight (dry) (mg)
Fibrin clot (60 second maturity) – daily exposure dose with physiological solution (control)	80,1±2,5
Fibrin clot (60 second maturity) daily exposure dose with chymopsin (5 mg)	30,2±2,6 p<0,001
Fibrin clot (60 second maturity) daily exposure dose with chymopsin (5 mg) by aminocaproic acid	41,3±8,8 p ¹ <0,01 p ² <0,05
Fibrin clot (900 second maturity) daily exposure dose with chymopsin (5 mg)	76,8±1,7 p>0,1

Note: p¹ – statistical significance of the variation from control parameter (physiological solution), p² – statistical significance of the variation from the parameter in the experiment with isolated chymopsin activity.

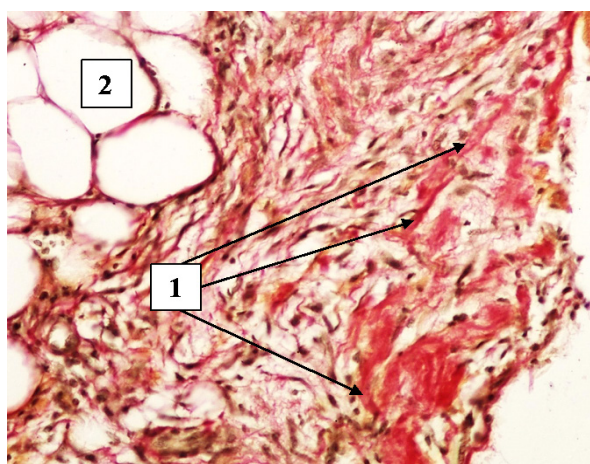


Figure 4. Microphoto Experimental reproduction of "fibrin" barrier in the retroperitoneal cellulose by injection of cryoprecipitate (5th day): 1 – fibrin of various maturity; 2 – fatty tissue. Van Gieson's staining, x 80 zoom

At the same time, the zone of formation of a "delimiting barrier" was characterized by the appearance of numerous fibroblasts, separate capillary vessels. Such histological picture is typical for the formation of local center of granulation tissue and is one of the conditions for further development of cicatricial encapsulation – tissue limitation of necrotic tissues and cyst formation.

In a clinical setting the terms of barrier formation and delimitation are significantly varied. First and foremost, they depend on the immunobiological state of the organism and presence of multi-organ failure. The matter is that enzyme toxemia has an expressed immunodepressive effect. The disorder of protein synthesis predetermines prolongation of barrier formation terms, while the depression of lymphoid element synthesis by sepsis does not favor their migration to the center of inflammation. Thus, modern adequate treatment contributes to the delimitation with cyst formation and fluid assembly in the retroperitoneal cellulose. There ex-

ists a group of patients with retroperitoneal necrosis which further develops into phlegmon of retroperitoneal cellulose, though by adequate therapy the number of such patients does not exceed 10 % of the total cohort. Consequently, the main trend in treatment of pancreatic necrosis is the delimitation of inflammation and cyst formation. Usually, according to the endoscopic ultrasonic examination, depending on the state of patient these terms range from 4 to 6 weeks.

The drainage of formed delimitation elements (false cysts and fluid assembly) is in the focus of the researches conducted in clinical setting by assistant Nasonov B.B. Types of drainage vary from trans-intestinal to paracentetic endermic or drainage through minimal access. Firstly, there was made the analysis of the results of transabdominal drainage of postnecrotic cysts in 26 patients with medium and severe forms of acute pancreatitis in the age from 28 to 64. These patients were operated after the formation of delimitation barrier and appearance of postnecrotic cyst in 3-4 weeks after the disease onset (sequestration phase of acute pancreatitis). After the formation of postnecrotic cysts there were made puncturing under US control with further insertion of 10 mm drainages for lavage and sequestrotomy. According to the results of dynamic US and fistulography, it was stated, that the cyst cavity collapsed after drainage gains irregular form. This can lead to not always total emptying with further abscess formation and requires extension of wound. Thus, 12 (46%) patients were exposed to reintervention with the extension of existing drainage wound up to 4-5 sm and resection of sequestra by open method through minimal access with substitution of drainages for the bigger ones. Respectively, the duration of hospital treatment of such patients was prolonged (averagely from $25,4 \pm 1,5$ to $38,1 \pm 2,1$ days). In 3 (11,5%) of them the conduction of repeated transcutaneous drainage under US control turned out to be sufficient. 11 (42,3%) patients out of 26 did not require reintervention. The clinical picture of the course of acute pancreatitis in all cases had positive dynamics. The duration of hospital treatment after the conducted minimal invasion constituted averagely $22,5 \pm 1,7$ days. Positive dynamics after transcutaneous paracentetic drainage of postnecrotic cysts and through minimal access was registered by dynamic US and CT of the abdominal cavity made during postsurgical period. The analysis of the treatment outcomes showed, that among the patients three died, which constituted (11,5%). They had developed the clinical picture of abdominal sepsis on the background of long-term treatment.

In recent years, we have implied trans-intestinal drainage in treatment of postnecrotic PG cysts. The method was introduced due to wide implementation of bolus MSCT and endoscopic ultra-

sonography (EUS) [19], which allow to evaluate the topographic anatomic distribution of postnecrotic cysts, their correlation with stomach wall, the degree of capsule maturity and its thickness (Figure 5).

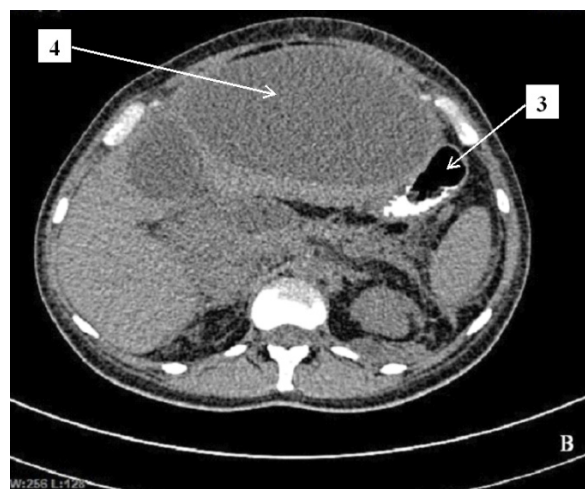


Figure 5.

Sterile pancreatic necrosis. MSCT of abdominal cavity (contrast per os): postnecrotic cyst (4), zone of attachment to the stomach wall (3)

We have examined the treatment of 26 patients. According to trans-abdominal US the formed capsule was revealed in 10 (45%) patients, according to MSCT – in 1 (4,5%) patient, by EUS – in 22 (90%) out of 24 patients. In 2 patients there were registered fluid assemblies, which differed from cysts by the lack of the wall on the background of inflammatory infiltration of surrounding tissues (Fig. 6a). EUS allows to determine not only the degree of delimitation of the forming cyst in the optimum way, but also the presence of sequestra in its cavity (Figure 6b).

Finally, by using Doppler mapping regime it is possible to choose a nonvascular section suitable for transgastral cyst emptying [20]. During the examination it is also possible to evaluate the diameter of Wirsung's duct and its correlation with the cyst. The procedure of transgastral drainage begins with the puncturing of stomach wall through nonvascular "route". Then in the point of content extraction, which is found in the area of cyst prolapse into the stomach, the stomach wall was burned through in the targeted point by cystotome and the cyst lumen was cannulated, there was made the PG enzyme sampling of content, cytological examination, bacterial flora incultation. Through the cystotome canal the guidewire was inserted into the cyst lumen, through it there was installed a 16-18 mm balloon after the removal of tube with further dilation of the whole in the posterior stomach wall. Then there was made the exploration and sanitation of cyst cavity, and if necessary – sequestrotomy. It should be mentioned, that there

is a risk of bleeding, that is why the whole should not exceed 1-2 sm. In cases, when it has a tendency to stricture formation, it is possible to be extended by a repeated balloon dilation or subsidiary incision (Fig. 7a) with the removal of sequestra

by means of a special trap-basket (Fig. 7б). The sanitation of cyst cavity and removal of free lying sequestra are reasonable to be done not earlier then in 2-3 days after drainage.

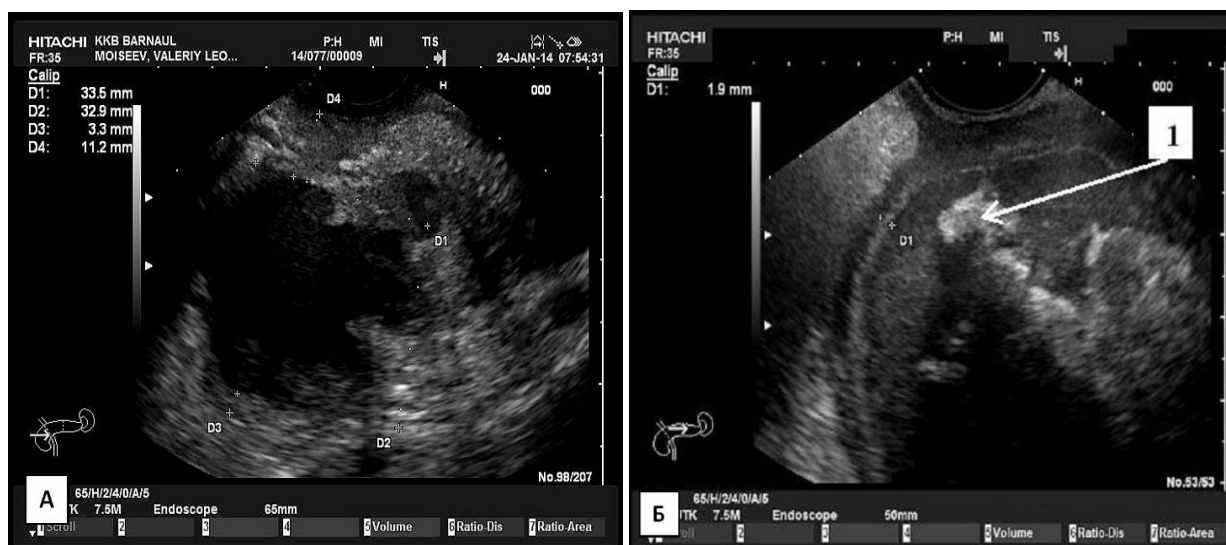


Figure 6. EUS

Sterile pancreatic necrosis. A – fluid assembly from infiltrate in parapancreatic cellulose without capsule.
 Б – postnecrotic cyst of peritoneal omental sac with formed walls (capsule) and sequestra (1)

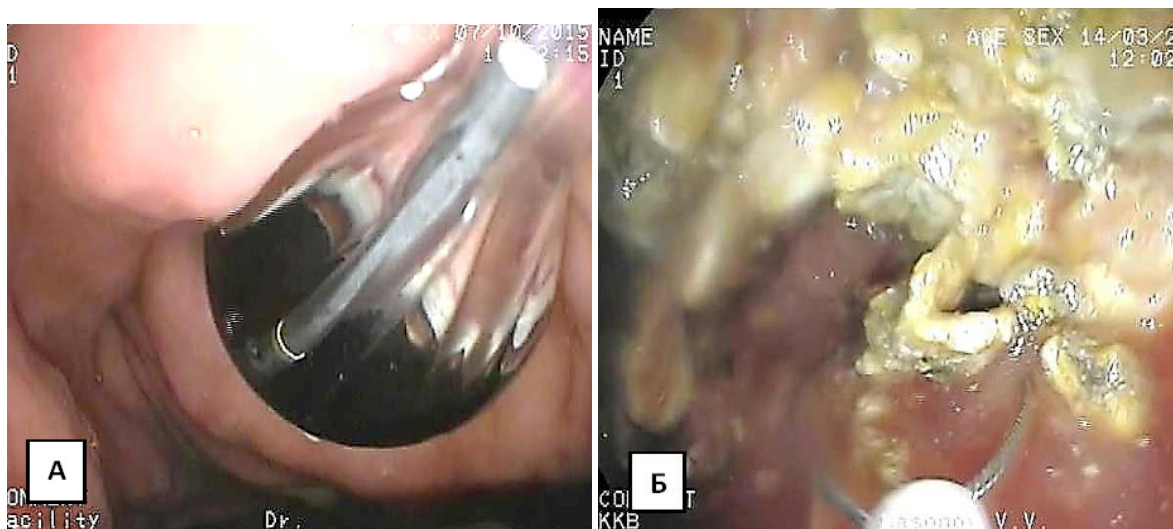


Figure 7. EUS

A – Balloon dilation of the whole in the stomach for cyst-gastroanastomosis formation by pancreatic necrosis.
 Б – Necrotic sequestrotomy through the formed cyst-gastroanastomosis

During postsurgical period there was performed dynamic observation with the evaluation of the state of anastomosis and cyst cavity on the 3rd, 7th and 14th day. By examination on the 3rd day there was registered the reduction of cyst-gastroanastomosis size, though the gastroscope easily enters the cyst lumen. By the observation in the cyst cavity there were seen the remnants of necrotic masses on the walls, the cavity lumen reduced considerably. On the 5th day, as a rule, there can be observed the diminution of cyst lumen and the reduction

of the cyst-gastroanastomosis diameter. To prevent early closure of anastomosis there is carried its balloon dilation leaving stents of “pigtail” type (Figure 8 a,b).

By the observation on the 14th day the cyst walls cleared totally, were covered with single fibrin strands, the cyst lumen reduced significantly. The endoscopic drainage of postnecrotic cysts was performed in 26 patients. 23 (87,5%) of them were with cyst, 3 (12,5%) patients had fluid assemblies on the background of PN. The average

period of postnecrotic cysts formation constituted 4,5 months. According to the visualization methods, cysts were localized: in 19 (73,07%) patients in the projection of the left sections of PG (body-tail), in 6 (23,07%) in the projection of right sections of PG. In 1 (3,86%) case the cyst of large and PG was not clearly visible. The sizes of fluid assemblies varied from 5.5 sm to 30.0 sm. Cystogastros-

tomy under EUS control was performed in 12 patients, in 3 cases – transgastral cyst stenting, in 9 patients – transgastral puncturing of cysts and fluid assemblies. The thickness of cyst capsule constituted $2,2 \pm 1,2$ mm. For all patients there had passed 6 weeks after the disease onset. Complications during postsurgical period were not registered. Cyst recurrence in long dates did not occur.

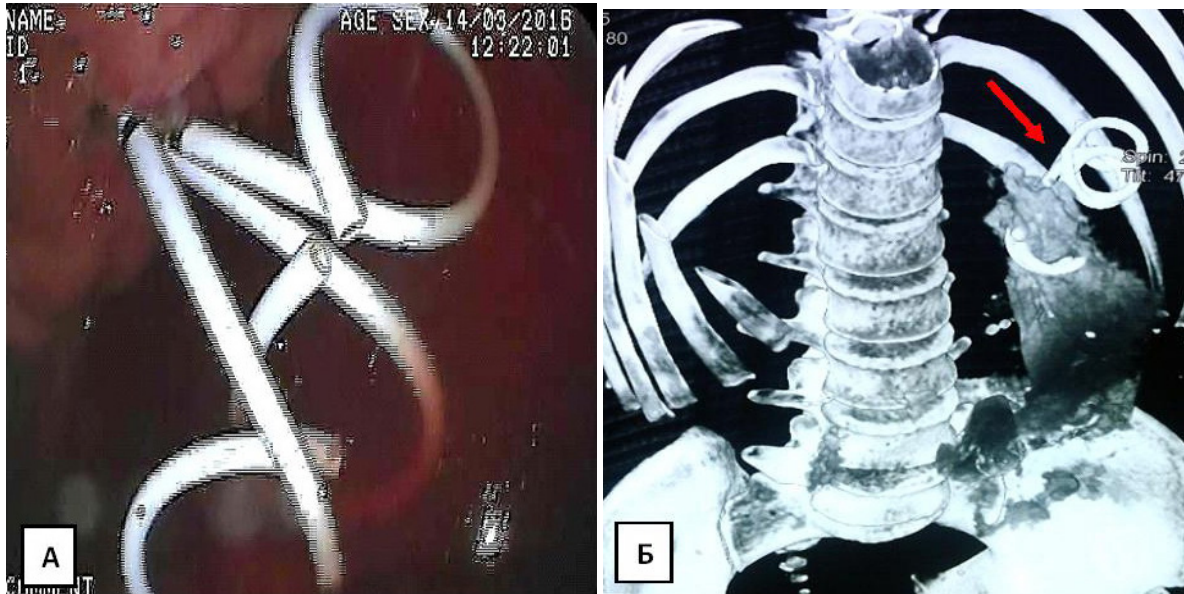


Figure 8. Sterile PN

Formed false postnecrotic cyst: A – EUS. Cyst-gastroanastomosis with inserted stents of “pigtail” type, B – MSCT of abdominal cavity (3D reconstruction). Location of stents draining the cyst (arrow)

Transgastral drainage under EUS control possesses a number of obvious advantages, the most important of which is the lack of laparotomy, sufficient emptying of cyst into the stomach lumen, additional lysis of sequestra by hydrochloric acid entering the cyst cavity from the stomach. Considering quick reduction of cyst size, it is also significant, that by the mentioned treatment method the length of patient’s stay in the hospital and treatment expenditures are reduced.

With respect to the obtained data, there arises the question of presence of open operations in pancreatic necrosis surgery. In our opinion, they can and should be implemented by septic phlegmons being the consequence of common retroperitoneal necrosis. However, open surgery is always accompanied by introduction of infection and is connected with the risk of abdominal bleedings in consequence of protracted bandaging, there is always a risk of spleen injure, vessel arrosion and formation of immature intestinal fistula. Finally, long-term treatment and contamination lead to abdominal sepsis with further disorders of blood coagulation system, risk of PATE, heart attacks and brain attacks.

Conclusion

1. Local rheological therapy allows to improve blood circulation in the vascular circulation of pancreatic gland and reduce the risk of necrosis progression.
2. The influx of enzymes from necrosis centers of pancreatic gland preconditions enzymic lysis of fibrin and hinders the process of delimitation in pancreatic gland and parapancreatic cellulose.
3. Formation of delimitation barriers in the form of fibrous capsule of cyst happens upon the expiration of 4 – 6 weeks of illness and can be stimulated by local implementation of fibrinogen donators.
4. Local transdermal and transgastral cyst and fluid assembly drainage leads to the reduction of mortality in comparison with open drainage methods.

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COMBINATION TREATMENT OF PATIENTS WITH CHRONIC PYELONEPHRITIS BY MEANS OF PELOOTHERAPY

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There were studied the possibilities of pelotherapy implementation in the combination treatment of patients with chronic pyelonephritis. It is shown, that the use of sulfide silt muds of Lake Mormyshanskoye has a positive effect on the course of latent inflammation stage of chronic pyelonephritis, allows to reduce clinical manifestations of the diseases, increases the percent of sterile urine culture, improves microcirculation in kidneys, the immune status of patients, cytokine profile of urine and blood serum, provides long-term anti-relapsing effect in 84% of patients.

Key words: chronic pyelonephritis, pelotherapy, combination treatment, sulfide silt muds, Bekhtemirskaya curative clay.

Kidney and urinary tract infection – is a numerous group within the structure of urological pathology ranking second among all human infectious diseases [1].

Chronic pyelonephritis is one of the most common infectious diseases of the urinary system [2, 3]. The most important task of modern urology is the elaboration and implementation of new more effective methods of treatment of chronic pyelonephritis [4].

It is known, that modern restorative treatment at the stage chronic pyelonephritis latent inflammation is able to terminate the pathological process, to postpone relapse for a long period of time and to achieve sustained remission. In order to reach a persistent therapeutic effect patients with chronic pyelonephritis for a long time have to take medications often causing allergic reactions and multiple organ failures [5, 6].

Natural therapeutic factors, as a possible reserve, are an important for the increase of chronic pyelonephritis treatment effectiveness [7]. The ability of pelotherapy to cause changes in many systems of the organism, influence the main elements of pathogenesis of the majority of diseases has been attracting clinical specialists' attention for a long time. At the present time, there are appearing scientific works proving the positive effect of pelotherapy on the course of chronic pyelonephritis [8]. However, the possibilities of pelotherapy to change the microcirculation of kidneys, humoral component of immune system, cytokine hemostasis and bacterial load of urine of patients with chronic pyelonephritis are still insufficiently studied.

Objective: to improve the effectiveness of treatment of patients with primary chronic pyelonephritis at the latent disease stage by means of including pelotherapy in the combination treatment.

Materials and methods

The current research included 73 female pa-

tients from 20 to 65 years old with chronic primary pyelonephritis at the stage of latent inflammation. The average age constituted 45,20±4,5 years. The average disease duration - 8,24±0,79 years, he duration of disease at the moment of appeal ranged from 3 to 18 years. The disease recurrence occurred in patients averagely 3,6 ± 0,2 times during 1 year.

The criteria of patient inclusion: primary chronic pyelonephritis (absence of developmental anomaly of the urinary system and disorders of urodynamics) at the stage of latent inflammation (mild or absent symptoms, minor laboratory manifestations, obligatory leukocyturia, bacteriuria), patients' consent to take part in the study.

The criteria of patient exclusion: chronic pyelonephritis at the stage of active inflammation or remission, presence of symptoms of intermittent or end stage renal disease, hydronephrosis, pyonephrosis; tuberculosis of the urogenital system; malignant and benign tumors of the urogenital system, all urological diseases at the acute stage; inflammatory diseases of the genital system, presence of other somatic and systemic diseases at the decompensation stage.

All patients were randomized by means of typological selection into 3 groups comparable by the main parameters – age, disease duration, clinical manifestations and presence of deviations in the urine analysis. The control group consisted of 22 healthy persons at the age from 20 to 65 years.

The patients of all three groups received medication therapy: antibacterial, spasmolytic, pain medication and phytotherapy. The patients of group 2 received an additional course of pelotherapy by Bekhtemirskaya clay in the kidney projection on the lumbar region. The patients of group 2 received an additional course of pelotherapy by curative sulfide silt muds of Lake Mormyshanskoye.

Before the treatment and on the 21th day of treatment all patients underwent a series of diagnostic measures, including the collection of clinical anamnestic data, general clinical laboratory examination,

ultrasound investigation of kidneys, determination of kidney microcirculation by means of LDF.

The method of clay and mud treatment was similar: peloid was heated on the water bath up to 40-45 °C. The patient was laid onto the therapy bed in the prone position. The 2 sm thick peloid was applied by means of traditional local application in the kidney projection on both sides, then the lumbar region was subsequently covered by the pack sheet, rubber sheet and blanket. Treatment time – 20 minutes. After the procedure the patient was washed by the shower of t –36 °C, rested for 30-40 minutes. The treatment course – 10 procedures, performed every second day.

The statistical data analysis was performed by means of Statistica v6.0, MS Excel 2007. The normality was estimated by means of the Shapiro-Wilk test. The factual data are presented in the form of “mean ± error of mean” ($M \pm m$). The comparison of independent samples was carried by means of Mann-Whitney U test, the comparison of samples before and after the treatment – by means of Wilcoxon test. The critical significance level by testing statistical hypothesis was taken to be equal to 0,05. In case of comparison of qualitative parameters in the linked samples there was used Cochran's Q test.

Results and discussion

The evaluation criteria of the effectiveness of treatment of the patients of all 3 groups were: clinical course of the disease, dynamics of laboratory parameters and evaluation of the functional state of kidneys. Thus, for all stated patients along with the basic laboratory blood and urine tests there was conducted the bacteriological urine analysis, was determined the concentration of G, a, M immunoglobulin, anti-inflammatory cytokines IL-1 β , TNF- α , IL-6 in blood serum and IL-8 in urine. To evaluate the functional state of kidneys there was performed a radiologic examination and there was indirectly stated the microcirculation of kidneys by means laser Doppler flowmetry.

According to the analysis of the results obtained by the examination of patients, there were determined the changes in the clinical blood analysis – the decrease of hemoglobin level, acceleration of erythrocyte sedimentation rate. The common urine analysis of 100% of patients showed a significant leukocyturia. Nechiporenko's test showed the increase of active and inactive leukocytes.

The bacteriological urine examination of the patients of all groups revealed a particular uro-strain, no sterile culture revealed. There was marked the prevalence of gram-negative microflora. In patients with primary chronic pyelonephritis there were registered *Escherichia coli* (47,94%), *enterococcus* (13,69%), *staphylococcus* (10,95%), *Klebsiella* (6,84%), *Enterobacter* (6,84%), *Proteus* (4,10%),

microbial associations of *Escherichia coli* with *staphylococcus*, *enterococcus* (9,64%).

By estimation of the humoral component of immune system initially before the treatment in patients with primary chronic pyelonephritis there was registered overproduction of IgG, IgM and reduction of IgA concentration in blood serum, which is considered as the imbalance of the humoral component of immune system, disorder of anti-infective resistance. The literature contains various data on the content of different classes of Ig by chronic pyelonephritis, but the most often case is the growth of IgG and IgM levels [9, 10].

The study of the cytokine profile of the patients showed a statistically significant increase of activity of anti-inflammatory cytokines (IL-1 β , TNF- α , IL-6) in blood serum and cytokine IL-8 in urine samples. As the ejection of IL-8 into urine is one of the activators of continuation of tubulo-interstitial inflammation in the urinary system, while the increase of IL-6 concentration in blood leads to the further sclerosis and cicatrization of kidney tissues, we can indicate the continuing inflammatory process in the urinary system [11].

Before the treatment in all three groups the disorder of microcirculation was characterized by the reduction of the microcirculation effectiveness index, index of shunting and myogenic tonus. All these changes indicate the reduction of blood perfusion intensity in the kidneys, ischemia, venous stasis on the background of inflammation in the renal parenchyma and congestive form of microcirculation disorder [12].

The most significant clinical effect was reached in group 3, as the clinical symptoms of chronic pyelonephritis were preserved only in 12% of patients, while in patients of group 1 and 2 – in 47,83% and 28% respectively.

The highest urine sanitation occurred in group 3, thus, by the analysis of bacteriological urine samples, exactly in group 3 there was observed the biggest number of sterile cultures in 88% of cases, in group 1 – 52,17%, in group 2 – 68%.

An expressed bacteriostatic effect of mud therapy should also be mentioned, as the degree of bacteriuria in positive urine cultures reduced: *Escherichia coli* – from 10^5 - 10^7 CFU/ml to 10^2 - 10^3 CFU/ml, *Staphylococcus epidermidis* – from 10^5 - 10^6 CFU/ml to 10^2 - 10^3 CFU/ml.

By the evaluation of microcirculation the maximum effect was obtained in group 3, which was expressed in the boost of blood flow, increase of perfusion, reduction of kidney tissue hypoxia. Such kind of therapy can restore the blood flow, eliminate ischemia of renal parenchyma and considerably improve the results of chronic pyelonephritis treatment.

The comparative evaluation of the study results allowed to state, that in group 3 after the treatment there was registered a lower level of IgG and IgM

in blood serum, lower levels of IL-1 β , TNF- α , IL-6 in blood serum and IL-8 in urine, consequently, a more expressed anti-inflammatory and immune-modulating activity.

The follow-up study of patients showed, that the duration of full clinical laboratory remission in patients with chronic pyelonephritis exposed to the course of combination treatment by curative silt sulfide mud of Lake Mormyshanskoye in 84% of cases constitutes more than 1 year, in groups 1 and 2 – 52,17% and 56% respectively. The disease recurrence in group 3 was registered 3 times rarer in comparison with the patients of group 1 receiving the course of standard medication therapy, and patients of group 2 receiving combination therapy by means of Bekhtemirskaya curative clay.

The obtained results are determined by the effects of curative mud: anti-inflammatory, immune-modulating, defibrosing, bactericidal and reparative-regenerative.

During the mud therapy procedure in the zone of mud application there occurs a long-term local skin hyperemia. Local hyperemia leads to the distention of vessels of the microcirculatory bloodstream and speeding of blood flow and lymph efflux of skin. Moreover, the activation of nonfunctioning capillaries and arterial venous anastomosis, increase of vascular permeability occur under the influence of biologically active substances effused by skin (histamine, bradykinin). The boost of blood flow in combination with the increase of vascular permeability and pH shifts contributes to the improvement of transportation of chemical substance dissolved in the mud, interstitial fluid outflow and oxygen flow to the cells [13].

Thus, the suggested curative complex including mud therapy proved its high effectiveness and reasonability of implementation in patients with primary chronic pyelonephritis at the stage of latent inflammation in order to prevent the progression of disease, prolongation of remission terms and to improve the life quality of patients.

The volatile substances, ions, lipoidotropic peptide and steroid hormone substances, humic acids and non-polar gas molecule (chemical factor) contained in the mud penetrate into the skin through the channels of sebaceous glands and hair follicles. Biologically active substances accumulated in skin improve the metabolism of subjacent tissues, increase excitability and conduction of skin nerve guides. Anti-inflammatory activity of curative muds manifests itself at the exudative and proliferative inflammation stages.

Humic acids and steroid containing peloid fractions having penetrated through epidermis at the exudative inflammation stage limit exudation and edema of tissues. In the area of inflammation they restrain the migration of leucocytes and edema due to the oppression of hyaluronidase destructive function. Increasing the activi-

ty of the components of the antioxidant system, they suppress peroxidation of lipids in the area of inflammation. Chemical components of curative mud suppress the polymerization of collagen fibres and boost the aggregation of glycosaminoglycans, mucoproteins and glycoproteids. As a result, the collagen producing function of fibroblasts decreases, which leads to the fibrosis slowdown [13].

Conclusion

Consequently, the implementation of pelotherapy in combination treatment of patients with chronic pyelonephritis positively effects the course of latent inflammation stage, allows to reach the reduction of clinical manifestations of the disease, increases the percent of sterile urine cultures, improves the kidney microcirculation, immune status of patients, cytokine profile of urine and blood serum and, thus, contributes to the prolongation of full clinical laboratory remission by more than 1 year in 84% of patients.

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OPTIMIZATION OF THE PROCESS OF ADAPTATION TO REMOVABLE LAMINAR DENTURES IN ELDERLY PATIENTS

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The article presents the analysis of the effectiveness of local ozone therapy in elderly patients using removable laminar dentures. Topical application of ozone contributed to the improvement of a number of clinical laboratory parameters of the tissue state of denture-bearing area and oral cavity, which generally increased the effectiveness of prosthetic treatment in patients using removable dentures and improved the long-term prognosis.

Key words: ozone, denture-bearing area, removable dentures.

Removable laminar dentures are widely used in prosthetic dentistry, although their negative effect on the tissues and organs of the oral cavity has been studied quite well [2]. Ozone therapy is one of the prospective methods of treatment in dentistry being a new and rapidly developing area of medicine [3]. The complex of ozone therapeutic effects allows to successfully apply it even in severe clinical cases [6, 7], thus, in our opinion, the use of this method in therapeutic treatment by removable dental prosthetics could also be quite effective.

Research objective: to optimize the process of adaptation to removable laminar dentures in elderly patients by means of local implementation of the ozonized olive oil.

Materials and methods

There was conducted the clinical laboratory study of the dental status in 92 elderly patients at the age from 60 to 70 years, who were exposed to prosthetics by removable laminar dentures for the first time. All participants of the research were divided into four groups: two study groups (23 patients in each group by partial and total teeth absence), in which during the first 10-14 days after the superimposition of removable laminar dentures there were performed applications of ozonized olive oil под under the denture base, and, respectively, two comparison groups.

There was evaluated the intensity of caries lesions according to DFM and DFM(f) indexes, the hygienic state of the oral cavity according to Fedorov-Volodkina index, the indexes of PMA and Myulleman-Sakser. There was also determined the level of cariogenicity of dental plaque according to Hardwik-Menlo modified by prof. Nedoseko. The study of functional parameters of salivary discharge included the determination of the speed of secretion of unstimulated saliva, its viscosity, pH and antioxidant activity. The cytological examination of the oral swabs from the denture-bearing area was performed along with the determination of indexes of differentiation and epithelial keratinization, and also the microbial cell adsorption reaction.

The blood supply level of the mucous membrane was evaluated by means of laser Doppler flowmetry. The microbiological study was conducted by traditional and instrumental methods with determination of the quantitative and qualitative microflora composition. There was also carried the analysis of questionnaires filled by patients during the process of removable denture use to determine the terms of adaptation. The qualitative data are presented in the form of Md; (Q1-Q3). The significance of the differences between the data was determined by means of Mann-Whitney U-test for independent groups, the differences were considered significant by $p \leq 0,05$. The analysis of the material was conducted by means of Statistica 6.0 programs (StatSoftInc., USA).

Results and discussion

The analysis of changes of DFM and DFM(f) indexes did not reveal significant differences between the groups. However, after the superimposition of removable dentures the hygienic state of oral cavity of the patients without additional treatment worsened during 1,5 months (2,4; 1,8-3 points), especially in comparison with the identical index in patients after the application of local ozone therapy (1; 1,3-1,83 points). Moreover, in patients of the study group the initial level of DFM index constituted 72%; 45-74%, and in 2 weeks of ozone implementation, despite the presence of removable laminar dentures in the oral cavity, it significantly lowered up to 48,5%; 33-55% ($p \leq 0,05$ in relation to the initial value), by 1,5 months – to 38%; 30-46% ($p \leq 0,05$ in relation to 2 weeks of study), increasing a bit by 3 months (45%; 26-56%), which generally indicates a significant reduction of gingival inflammation. Against this background, the dynamics of the values of gingival bleeding index in patients of the study group also turned out to be significantly positive, which corresponds to the data of literature [1, 4, 5].

The analysis of the cariogenicity of dental plaque indicated its significant decrease (1,83; 1,4-2,1 points at the initial level, 1,3; 1,1-1,8 points – in 14 days, $p \leq 0,05$ in relation to the initial value). The re-

sults of the microbiological study demonstrated significant differences in the state of microflora of the oral cavity against the background of local ozone therapy and without. Namely: the presence of removable laminar dentures without additional treatment (group of comparison) in the majority of cases lead to the growth of CFU (colony-forming

units) of already existing representatives of normal flora, and in a number of cases – to the appearance of new strains. The patients of the study group showed the stable composition of microflora due to the soft antibacterial effect of low ozone concentrations (Figure 1).

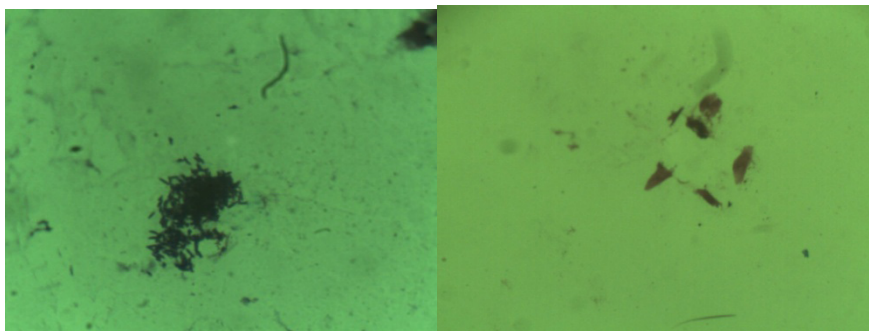


Figure 1.

Reduction of bacterial content of the oral cavity by local ozone therapy (left – before treatment, right – in 10 days after treatment), X100 zoom, hematoxylin and eosin staining

The study of the speed of saliva secretion and its viscosity did not reveal significant differences among the patients of the compared groups. In the majority of patients the speed of saliva secretion increased during the first 2 weeks after the superimposition of dentures against the background of the decrease of its viscosity. By 3 months the speed of saliva production lowered, the viscosity, on the contrary, grew. However, there were observed significant differences in pH values of the oral fluid registered in long terms (higher values in patients exposed to local ozone therapy). The study of the antioxidant activity of the oral fluid showed the higher level in patients after ozone implementation and depletion of antioxidant reserves by traditional prosthesis.

The cytological study showed that in patients of the study group local ozone therapy had a favorable effect on the epithelial state of the mucous membrane of the denture-bearing area, which was expressed in the growth of the degree of its differentiation and preservation of the initial level of keratinization. Nonspecific resistance of the mucous membrane determined by the microbial cell adsorption reaction increased significantly after the conducted treatment. The dynamics of the blood supply level of the mucous membrane of the denture-bearing area is presented in Table 1.

According to the questionnaire analysis, generally, the terms of adaptation in case of local ozone therapy reduced to by 26,5% by partial and 26,3% by total removable prosthesis.

Table 1

Influence of local ozone therapy on the dynamics of perfusion index (M, pf.u.) of the mucous membrane of the denture-bearing area in elderly patients by prosthetic treatment by removable laminar dentures

Studied groups Initial value		Terms of study				
		14 days	1,5 month	3 months	6 month	
Patients with partial removable dentures, n=46	Study group, n=23	20,21; 19,87-24,3	20,26; 20,1-25,2*	20,24; 20,12-23,6*	19,5; 18,5-20,26*	18,6; 17,4-21,3
	Comparison group, n=23	20,46; 20,01-25,1	19,24; 18,7-26,3	19,2; 17,23-21,14	18,06; 17,23-20,01**	17,8; 16,5-19,52**
Patients with total removable dentures, n=46	Study group, n=23	22,1; 18,9-24,2	21,7; 19,8-25,1*	20,8; 19,5-22,1*	19,2; 17,4-21,3	18,2; 17,1-19,6
	Comparison group, n=23	21,04; 18,21-23,25	20,14; 18,45-23,12	19,2; 17,5-20,91	18,6; 17,2-19,6**	17,2; 16,4-18,9

Note: * - significant differences in relation to the comparison group, $p \leq 0,05$, Mann-Whitney U-test for independent samples, ** - significant differences in relation to the initial level, $p \leq 0,05$, Mann-Whitney U-test for independent samples.

The analysis of the obtained results showed, that by traditional prosthetic treatment of patients with removable laminar dentures there occur numerous negative changes of clinical laboratory indexes of the state of oral cavity: worsening of the hygienic state, increase of gingival inflammation spread, disorders of natural processes of the oral mucous cavity regeneration and blood supply, some shifts of the functional parameters of salivary discharge and reduction of the antioxidant ability, and also the indications of microbial imbalance of the oral cavity.

The majority of the examined patients showed a significant improvement of the hygienic state of the oral cavity after the course of ozone therapy, which was evaluated according to Fedorov-Volodkina index in patients with partial removable dentures, while in patients with total teeth absence it was evaluated according to the state of the dentures itself by Ambjornsen method. The obtained effect in patients with partial denture defects is presumably connected with the reduction of the activity and adhesive ability of the mucous microflora (which is indirectly confirmed by the reduction of the caries activity of dental plaque). The influence can also be caused by the direct cleaning effect of ozone due to oxidation and decay of dental plaque organic components. The decrease of activity and spread of inflammatory processes in periodontal tissues also plays a role, which enables the conduction of hygienic measures for patients at home.

The expressed positive effect of local ozone therapy was observed by the study of gingival state. Such results are explained by the influence of ozone directly on several pathogenetic elements of periodontal disease, namely: reduction of inflammation, improvement of capillary blood flow, activation of antioxidant defense system, antimicrobial effect, especially expressed by the influence on the anaerobic flora playing an important role in the development of periodontitis.

The analysis of the antioxidant ability of mixed saliva showed that in patients with removable laminar dentures the antioxidant defense grew significantly after the course of ozone therapy with further preservation of this level and in long terms. The stated effect is determined by the stimulation effect of ozone as the source of active oxygen forms on the production of enzymes of antioxidant defense. Further, after the end of the treatment course, this effect plays an important role in the realization of long-term results of ozone therapy, as the pathogenesis of numerous pathological conditions in the oral cavity includes imbalance of pro- and antioxidant systems.

The cytological study revealed significant differences in the epithelial state of the mucous membrane of denture-bearing area in patients both with partial and with total removable dentures.

The stated changes allow to assume that ozone has a favorable effect on the regeneration of mucous membrane due to the improvement of tissue microcirculation, tissue oxygenation, activation of oxygen depending enzymatic processes and reduction of inflammation. To our mind, the stated results are extremely important for the solvation of the problem of adaptation of patients to removable dentures, as their negative effect, first of all, is reflected on the mucous membrane of the denture-bearing area, which is initially not intended for functioning in such conditions.

The data of laser Doppler flowmetry, which were used to evaluate the parameters of tissue microcirculation in the mucous membrane of the denture-bearing area, showed an expressed positive effect of the ozone therapy. These data are explained by such ozone effect as biochemical activation of the functions of erythrocytes, increase of cell membrane flexibility, improvement of tissue oxygenation (including the endothelium of blood vessels), activation of nitrogen oxide synthesis, which leads to the vascular distention.

The analysis of the results of microbiological study showed, that in patients of the study group at early stages (14 days, 1,5 months) there had not been revealed significant shifts in the qualitative and quantitative microflora composition. This was expressed in the principal preservation of the initial strains indicated before the treatment, and also preservation or slight reduction of their titers. The current results show, that despite the express bacterial ozone effect, by particular schemes of its implementation (such as presented in the study) it can be used not only to suppress pathogenic strains by the already developed pathology, but also by particular concentrations for the prevention of unfavorable shifts in the qualitative and quantitative composition of the resident microflora. Thus, there is realized the preventive function of ozone consisting in the prevention of microbial imbalance and further – of various diseases connected with it.

The results of questionnaire implied for subjective evaluation of the process of patients' adaptation to removable dentures showed high effectiveness of the ozone therapy. Such conclusion can be made on the basis of lower occurrence and quicker disappearance of key complaints appearing in patients during the denture use. Predominantly, due to the above state positive effects, the most significant difference between the patients of the study and comparison groups referred to such complaints, as pain under the denture, disability to chew, irritation due to the presence of the denture.

Conclusion

Thus, the results of the carried study allow to draw a conclusion on a significantly positive effect of local ozone therapy on a number of clin-

ical laboratory parameters of oral cavity in elderly patients using removable laminar dentures, namely: improvement of the hygienic state of the oral cavity and the dentures, significant reduction of gingival inflammation in the area of remaining teeth, acceleration of regeneration of epithelial mucous membrane of oral cavity and preservation of the initial level of its blood saturation, stabilization of the qualitative and quantitative composition of normal microflora and antioxidant ability of the oral fluid. In total, these data allow to state the effective influence of ozone on the process of adaptation to removable dentures.

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IMPLEMENTATION OF MODERN TECHNOLOGIES IN COMBINATION TREATMENT OF POLYTRAUMA PATIENTS WITH DOMINANT CHEST TRAUMA

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Mutual aggravation of state by polytrauma considerably complicates the diagnostic and treatment process, delaying the provision of specialized help, for example, by concomitant craniocerebral and thoracic trauma or skeletal injuries and chest injuries, there are imposed stringent requirements for choosing the amount of diagnostic and therapeutic measures.

Research objective: the improvement of the efficiency of combination treatment of patients with severe concomitant injury with dominant chest trauma by means of minimally invasive methods of treatment.

There was elaborated a diagnostic and treatment algorithm of management of patient with SCCT. There are defined indications for emergency thoracotomy, emergency and urgent video-assisted thoracoscopy, local fibrinolytic therapy by clotted hemothorax and post-traumatic are formulated at curtailed hemothorax and posttraumatic pleural empyema, valvular bronchial blockage by tension and long-term pneumothorax, indications for osteosynthesis of fragment rib fractures by angle stable plates.

The implementation of minimally invasive methods allowed to reduce the number of operated patients and increase the number of discharged recovered patients.

Key words: *severe concomitant injury with dominant chest trauma, hemothorax, pneumothorax, fragment rib fractures, treatment.*

Mutual aggravation of state by polytrauma considerably complicates the diagnostic and treatment process, delaying the provision of specialized help, for example, by concomitant craniocerebral and thoracic trauma or skeletal injuries and chest injuries, there are imposed stringent requirements for choosing the amount of diagnostic and therapeutic measures [1, 2, 3, 4].

Objective: the improvement of the efficiency of combination treatment of patients with severe concomitant injury with dominant chest trauma (SCCT) by means of minimally invasive methods of treatment.

Materials and methods

There were analyzed the results of treatment of 263 patients with SCCT being under medical treatment in the Federal State Budgetary Healthcare Institution "Regional Clinical Hospital of Emergency Medical Care". Male patients constituted 208 (79,0%), female patients – 55 (21,0%). The age of patients ranged from 15 to 79 years. The causes of trauma were various. The most common cause of SCCT were road accidents - 97 (36,8%) patients. Less common were home accidents - 72 (27,4%), criminal accidents - 50 (19,1%), occupational accidents - 30 (11,4%) and falls from height 14 (5,3%).

The majority of patients were taken to the department of severe concomitant injury during the first two hours since getting injured - 152 (57,9%),

during the period from 3 to 24 hours - 55(20,9%), from 24 to 72 hours - 39 (14,8%), in 72 hours - 17 (6,4%).

The estimation of the injury severity was performed according to ISS scale [5]: in 109 (41,5%) patients it was under 25 points, in 120(45,6%) – from 25 to 40 points, and in 34 (12,9%) – over 40 points.

Out of 263 patients 109 (41,5%) patients were included into the main group, 154(58,5%) – into the comparison group. The patients of the main group were exposed to modern minimally invasive interventions (differentiated local fibrinolytic therapy, valvular bronchial blockage, video-assisted thoracoscopy (VTS), rib osteosynthesis by angle stable plates). Patients of the comparison group received conventional treatment (blind thoracostomy, thoracotomy, etc.).

Unilateral thoracic injuries were registered in 219 (83,2%) patients, bilateral – in 44(16,8%). In 198 (75,2%) patients chest trauma was accompanied by subcutaneous and intermuscular emphysema. The groups were comparable to each other according to the stated parameters.

The type of intrathoracic complications in the examined patients is presented in Table 1.

In the overwhelming majority of cases severe chest trauma by concomitant injury was accompanied by multiple fractures of ribs and other chest bones, which lead to the deformation of rib cage, mechanical acute and/or contusional effect on internal organs (Table 2).

Table 1

Complications of polytrauma patients with dominant chest trauma

Complications	Groups				p	Both groups	
	main		comparison			abs. number	%
	abs. number	%	abs. number	%			
Pneumothorax	40	36,8	55	35,7	>0,5	95	36,1
Hemothorax	21	19,2	28	18,2	>0,5	49	18,6
Hemopneumothorax	48	44,0	71	46,1	>0.5	119	45,3
Total:	109	100	154	100		263	100

Table 2

Chest fractures in patients with SCCT

Fractures	Groups				p	Both groups n=263	
	Main n=109		Comparison n=154			abs. number	%
	abs. number	%	abs. number	%			
3-6 ribs	75	68,8	84	54,5	>0,5	159	60,4
More than 6 ribs	34	31,2	70	45,5	>0,5	104	39,6
Fragment rib fractures with thoracic wall floatation	17	15,6	46	29,8	>0,5	63	23,9
Thoracic vertebra	14	12,8	24	15,5	>0,25	38	14,4
Breast bone	7	6,4	6	4,8	>0,5	13	4,9

We elaborated the diagnostic and treatment approach to the management of SCCT patients. Indications for emergency thoracotomy were considered big and total hemothorax, hemopericardium with cardiac tamponade, hemomediastinum with compression of respiratory passages and major vessels, major chest penetrating wound with открытым пневмотораксом and massive pulmonary injury. Indications for emergency VTS were injuries of the "thoracoabdominal zone", middle and small hemothorax, post-traumatic pleural empyema.

Emergency VTS was conducted by continuous intrapleural bleeding with blood effusion into drainages over 200ml/hour and absence of signs of hemostasis [6]. By clotted hemothorax and formation of post-traumatic empyema with pleural cavity segmentation there was implemented differentiated local fibrinolytic therapy. By tension and long-term pneumothorax not eliminated by drainage (during 4-5 days) there was used valvular bronchial blockage [7,8]. By multiple fractures of ribs with deformation of rib cage accompanied by paradoxical respiration, there was conducted open reduction of rib fractures by rib valve and osteosynthesis by angle stable plates.

Local fibrinolytic therapy was performed by means of streptokinase medicines. The dose of streptokinase constituted 1500000 IU. The drug

was dissolved in 20 ml physiological solution and injected into the pleural cavity. The exposition in pleural cavity constituted 3-24 hours, after what the drug and exudate were removed, and the pleural cavity was washed by antiseptic solution. The introduction of fibrinolysis activators was made daily or in a day, 1-3 time in total. By the reduction of plasminogen activity in the pleural exudate up to lower than 7% there was implied the method of intrapleural injection of streptokinase with fresh frozen plasma elaborated in the hospital [9]. The amount of removed exudate ranged from 50 to 2000 ml per day.

In order to fuse the pulmonary-pleural fistula by pneumothorax we have elaborated and clinically approved the method of the fistulous bronchus occlusion by an original endobronchial valve (registration certificate № 01.03.2006 (5625-06 of 21.12.2006).

VTS was performed under operating conditions under endotracheal anesthesia without separate bronchus intubation.

To restore the ribcage and eradicate paradoxical respiration of the rib valve there was performed open reposition and osteosynthesis of fragment rib fractures by angle stable plates under endotracheal anesthesia. Osteosynthesis was conducted in the first two days.

Results and discussion

By the comparison of results of treatment of clotted hemothorax in the 2nd group (with intrapleural injection of streptokinase, 23 patients), recovery was observed in 15 (65,2%) patients, chronization of process – in 8 (34,8%), 6(26,1%) of whom were further operated. In the 1st group of patients exposed to intrapleural fresh frozen plasma injections activated by streptokinase (15 patients), 14(93,3%) patients were dismissed after recovery, in 1(6,7%) patients there was registered the carbonization of process, further he was operated. The number of discharged recovered patients. in the 1st group was 1,4 times higher (p<0,02).

Anteriolateral thoracotomy for continuous intrapleural bleeding, suspected heart wound or thoracoabdominal injury was performed in patients of the main group in 3 (3,8%) cases, in patients of the comparison group – in 14(12,5%) cases (p<0,05).

Valvular bronchial blockage in patients with post-traumatic pneumothorax was preformed in 11(32,4%) patients. The duration of occlusion of the fistulous bronchus occlusion in the main group constituted averagely 21,3+2,7 days. Combination treatment of post-traumatic pneumothorax in all patients of the main group allowed to reach lung expansion and closure of pulmonary-pleural fistula. In the comparison group 4(7,8%) patients were operated for persistent pneumothorax and functioning bronchopleural fistula.

The implementation of the elaborated algorithm of patient management allowed to reduce the number of operated patients by 3,8 times, increase the number of discharged recovered patients by 1,4 times.

Out of 63(23,9%) patients with multiple fragment rib fractures with thoracic wall floatation the osteosynthesis of ribs of was conducted in 17(26,9%) patients, in all patients there was restored the rib cage and stabilize “paradoxical respiration” of the rib fragment. Total duration of artificial lung ventilation after osteosynthesis constituted averagely 3,2+0,8 days. While by conventional treatment its duration by fragment rib fractures was 9,2+0,6 days (p<0,001). No postoperative complications were registered.

The implementation of rib osteosynthesis by multiple fragment rib fractures with thoracic wall floatation allowed to reduce the duration of artificial lung ventilation by 2,8 times.

The elaborated technology of management of patients with severe concomitant injury with dominant chest trauma allowed to increase the number of discharged recovered patients by 1,3 times (p<0,05) and to reduce the number of chronic patients by 2,1 times (p<0,05) (Table 3).

Long-term results of treatment of the majority of SCCT patients were traced within the terms from 6 months to 4 years.

Table 3

Immediate results of treatment of patients with SCCT by means of minimally invasive technologies

Indexes	Groups				p
	Main		Comparison		
	abs. number	%	abs. number	%	
Recovery	75	68,8	83	53,8	<0,05
Chronization	11	10,0	33	21,4	<0,05
Died	23	21,2	38	26,7	>0,25
Total	109	100	154	100	

Table 4

Long-term results of treatment of SCCT patients by means of minimally invasive technologies

Indexes	Groups				p
	Main		Comparison		
	abs. number	%	abs. number	%	
Recovery	55	87,3	40	61,5	<0,01
Chronization	4	6,3	18	27,7	<0,002
Died	4	7,3	7	10,8	>0,5
Total	63	100	65	100	

At late times the number of recovered patients in the main group was by 25,8% higher than in the comparison group (p<0,01). The number of chronic patients in the main group was by 5,0

times lower than in the comparison group (p<0,002) (Table 4).

To illustrate the efficiency of minimally invasive methods in treatment of polytrauma patients with

severe chest injury there is presented the clinical observation.

A 22-year-old patient was admitted to the hospital on 07.09.2011 in 1 hour 20 minutes after the occupational trauma (was covered with soil in a trench) with complaints of intensive chest and stomach pains, dyspnoea at rest, dizziness, expressed fatigue.

Upon admission, the state of patient was extremely severe. Pale skin cover with cold sweat, cyanosis of nasolabial triangle, fingers and toes. The number of breaths – 36 times per 1 minute. Arterial blood pressure – 80/40 mm.hg. Pulse – 120 beats per minute, obscure. X-ray radiography of breast: lungs collapsed on both sides, pressed against the hiluses, mediastinum not shifted, sinuses unrevealed (Figure 1).

The patient underwent laparoscopy – in the abdominal cavity there were discovered 500 ml liquid blood, multiple ruptures of the right lobe of liver, primarily on the diaphragm surface.

On the basis of clinical data, laboratory and instrumental examination methods, there was established a diagnosis: severe concomitant trauma, blunt chest trauma, bilateral post-traumatic hemothorax, blunt intraabdominal injury, multiple fractures of the right lobe of liver, hemoperitoneum, hemorrhagic shock of degree III.

The patient's state corresponds to 42 points according to ISS (injury severity score).

The patient was operated for emergency indications. There was made the drainage of the right pleural cavity in II intercostal space along the midclavicular line and in VI intercostal space along the back axillary line and of the left pleural cavity in II intercostal space along the midclavicular line. The laparotomy was performed. The abdominoscopy showed multiple fractures of the right lobe of liver, primarily on the diaphragm surface, with intensive bleeding, round and falciform ligament of liver are ruptured. There was conducted the sealing of liver ruptures.

The drainages of the right pleural cavity indicated an intensive air and blood shunt. Per 1 hour there were released about 400ml blood, positive test of Ruvilua-Greguara. Under intubation anesthesia there was performed anteriolateral thoracotomy in VI intercostal space on the right. The abdominoscopy showed multiple fractures and of the lower and middle lobes of the right lung with intensive bleeding. There was conducted an atypical resection of the lower and middle lobes of the right lung and suturing of the upper lobe of the right lung. During the operation there was registered expressed bleeding.

The patient was admitted to the intensive therapy unit for extended artificial lung ventilation and inotropic support.

12.09.2011 – the patient's condition worsened, hemoperitoneum and subacute peritonitis were

diagnosed, therapeutic relaparotomy was performed. In all areas of abdominal cavity there was revealed lysed blood, in the lesser pelvis and down the right flank there were deleted blood clots. Small intestine is swollen up to 5cm in diameter, on the serous membrane – fibrin assemblies. There was performed the decompression of small intestinal content into the large intestine.

19.09.2011 – the X-ray radiography of thoracic organs revealed free fluid in the right pleural cavity not diffuent by X-ray radiography in prone position (Figure 2).

The computer tomography of thoracic organs of 20.09.2011 revealed the reduction of the right lung volume due to the resection of lower and middle lobes and the presence of free air in pleural cavity. The observed lung tissue with areas of infiltration.

Ultrasonic scanning revealed the presence of fluid in pleural cavity with hyperechogenic inclusions and fibrin, signs of clotted hemothorax on the right (Figure 4).

By the puncture of the right pleural cavity there was obtained a small amount of laky blood with clots. 20.09.2011 – to eliminate clotted hemothorax there was made an injection of 50 mg Actilise into the pleural cavity. 21.09.2011 – drainage of the right pleural cavity in VI intercostal space along the scapular line, through the drainage there were released 900 ml laky blood. The control X-ray radiography of 22.09.2011: right lung partially collapsed, small amount of fluid with horizontal level on the right (Figure 5).

Ultrasonography of pleural cavity: on the right side of pleural cavity there was located small amount of fluid with linear inclusions, small pleural fillings (Figure 6).

Considering the severity of condition, the preserved intensive air shunt through the drainages from right pleural cavity, on 21.09.2011 there was performed bronco-fibrosopy under local anesthesia and insertion of the endobronchial valve №15 into the intermediate bronchus, air shunt through the drainage reduces considerably, in 4 days – terminated.

After valvular bronchial blockage the patient continued to receive the course of massive antibacterial therapy, cryoplasm-antienzyme complex, infusion and detoxication therapy. During 8 days the hemodynamics was sustained by sympathomimetic infusion. For 10 days the patient was exposed to extended artificial lung ventilation. In the intensive therapy unit and surgical department the patient received 2700 ml polyglucin, 2800 ml rheopolyglucin, 2040 ml one-group erythrocyte concentrate and 3400 ml fresh frozen plasma.

20.10.2011 – broncofibrosopy there was performed. The bronchial blocker was deleted by biopsy forceps. The mucous membrane of the intermediate bronchus at the point of blocker presence

was characterized by slight edema and hyperemia. X-ray radiography of thoracic organs of 22.10.2011: on the right the front costodiaphragmatic sinus is shaded, agraftes in the root, lung tissue expanded. On the left no focal and infiltrative shadows (Figure 7).

The patient was discharged with improvement. Examination was performed in 2 and 10 months, healthy (Figures 8, 9).

Thus, the current study shows, that the implementation of minimally invasive methods in combination treatment of hemothorax and pneumothorax in the patient with concomitant severe trauma contributed to the recovery of the patient.

Conclusion

The implementation of minimally invasive methods allowed to improve the effectiveness of combination treatment of polytrauma patients with dominant chest trauma.

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THE USE OF STATISTICAL STABILOMETRIC METHOD FOR ASSESSING POSTURAL DISORDERS IN PATIENTS WITH PARKINSON DISEASE

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Postural disorders are among the most disabling clinical symptoms of Parkinson's disease (PD). Objective: To estimate the regulation of motor activity in PD patients and their relatives via stabilography method to create a risk assessment PD algorithm. Materials and methods. Clinical and neurophysiological analysis was performed in 25 patients with PD, 9 relatives of patients and 31 people for control group without any clinical manifestations of neurological diseases. All surveyed produce static stabilometric study. The results show a significant reduction in compensatory ability to maintain balance and the main pillar in Parkinson's disease, regardless of the clinical form of the disease. Stabilometric method can detect violations of the regulation of motor activity in healthy people at risk of PD.

Key words: Parkinson's disease, Stabilometric method.

The Parkinson's disease (PD) is an irreversibly progressing neurodegenerative disease based on the predominant damage of dopaminergic neurons of substantia nigra (SN) presented in combination of hypokinesia and muscular rigidity, shivering, postural instability and a broad range of non-motor symptoms [1]. It is stated, that PD clinical manifestations are diverse and include vegetative, sensory and neuropsychic disorders along with the motor ones. At the present time, the spectrum of non-motor symptoms is considered as PD predictor having a lead of more than 10-20 years [2]. Moreover, the intensity of motor symptoms has a stronger influence on the patients' quality of life than the intensity of non-motor clinical manifestations [3].

At the late stages, the diagnosis of PD does not cause difficulties not only for neurologists, but also for the doctors of other specialties. At present, a serious problem is still the diagnostics of the disease at early stages, when the motor defect is minimally expressed and the treatment of pathology is most effective. According to the epidemiological study of Goncharova Z.A. et al. (2014), in the city of Rostov-on-Don, out of all patients with PD registered at the healthcare institutions of the city only 8,1% are diagnosed with the I stage. At the same time, patients with the II stage constitute 41,6%, with the III stage – 40,37%. According to the authors, such a low epidemiological indicator of PD I stage frequency of occurrence is connected with the insufficient diagnostics of the current disease at the early stage [4].

The main PD manifestations include walking and postural resistance disorders which develop at a particular stage in all patients [5]. At the early disease stages, walking disorders, as a rule, do not cause any serious problems in patients, but with the PD progression and postural instability

their influence grows consistently accompanied by the appearance of "freezing", falls, which finally leads to the inevitable patient's disablement [6]. The disorder of balance function increases the possibility of falls either by standing or by moving of patients, contributes to the appearance of fractures, growth of functional dependence of patients, decreases their quality of life. Apart from the falls, postural disorders are characterized by the change of the muscle tone, which leads to the development of the flexion pose, in severe cases there can develop camptocormia – expressed bendover of the body to the front. A number of patients are characterized by the development of the Pisa syndrome, by which the body diverges in the coronary plane. Postural disorders also include microbasia, freezing during walking, propulsions [7, 8].

The appearance of modern instrumental methods of examination of walking and balance functions allows to study the peculiarities of walking and postural stability disorders at different stages of PD in more detail. One of such methods is stabilography combining such advantages as noninvasiveness, possibility of automatic processing, ability of mass use. The principle of stabilography method consists in the evaluation of human biomechanical indicators during the process of keeping the vertical pose [9].

The keeping of balance by human is a dynamical phenomenon requiring continuous movement of the body which is the result of interaction of vestibular and visual analyzers, articular and muscular proprioception, central and peripheral nervous system. It should be noted, that the conditions of the vertical pose maintenance are characterized by a special difficulty – small bearing area, great number of turning joints and high position of the gravity center. Maintenance of the vertical pose involves high number of various reflectory

systems forming a complicated system of regulation [10].

Until the present time, there has not existed a single viewpoint on the mechanisms of postural instability development by PD.

At the moment, there is marked the accumulation of PD cases in families. By the existence of one close relative with PD, the risk of this disease increases by 2-2,5 times, while by the existence of two relatives with PD the risk grows nearly by 10 times. In this regard, the evaluation of PD risk in patients' relatives becomes topical. As PD refers to the diseases with genetic predisposition, essential is also the problem of the search of early symptoms forming the clinical picture of the disease.

Research objective: estimation of the regulation of motor activity in PD patients and their relatives via stabilography method.

Materials and methods

The research was performed on the base of the neurological department of the SBEI HPO RostSMU hospital during the period from March 2016 to November 2016. By the study there were used the data of anamnesis, medical documentation, full neurological and instrumental examination of 25 patients with PD (14 men, 11 women), 9 relatives of probands (4 men, 5 women) and 31 persons for the control group (13 men, 18 women).

The stabilographic study was performed in the laboratory of extreme physical methods of diagnostics and treatment of RostSMU. The stabilometrics was conducted in the specially equipped room with sufficient area (20 m²) to prevent acoustic orientation of patient in the space in the presence of the doctor-researcher. The patient's feet were placed on the platform according to the American position. From the moment of patient's readiness until the start of the examination there was kept the interval of not less than 20 seconds to avoid the change of parameters due to transition processes. The Romberg's test consists of three tests – maintenance of balance with open (OE) and closed (CE) eyes and the Target test (T).

In terms of the first test, the examined person had to stand in the normal position with open eyes during 52 seconds with the following task: to calculate inwardly the circles of white color appearing on the display. In the second test, the examined person stood in the normal position with closed eyes and counted sound signals. The essence of test with closed eyes consists in the fact, that the visual analyzer influence is excluded and the vertical position is retained only due to proprioception. Test T was performed in one stage with visual feedback. The examined person standing on the platform should keep the marker in the center of the target with large scale of reflection by moving the body.

The test was interrupted and started again by the appearance of distractors capable of changing the results: coughing, scratching, head turning, any speech, external audio and other signals. Upon the end of the test the examined person reported the number of circles and signals. According to the test results, there was calculated the Romberg coefficient as the relation of the area of statokinesiogram in the test with closed eyes ELLS (CE) to the area of statokinesiogram in the test with open eyes ELLS (OE). Romberg coefficient = $ELLS(CE) / ELLS(OE) * 100\%$; is used for the quantitative determination of the correlation between the visual and proprioceptive systems of balance control in the normal position.

The statistical processing was performed by means of Microsoft Office Excel 2007 (Microsoft Corp., USA). The character of data distribution was evaluated by the graphical method. The data with normal distribution were processed by parametrical methods of the statistical significance evaluation: Student t-test (t-test). In case of data distribution deviating from the normal one, there was used the non-parametric Mann-Whitney U test (U-test). The critical significance level by the testing of statistical hypothesis was considered 0,05. The description of characteristics with normal distribution is presented in the form of $M \pm SD$, where M - arithmetical mean, SD – standard deviation.

Results and discussion

In the analyzed sample the average age constituted $62,3 \pm 7,7$ years, the stage according to the Hoehn and Yahr Rating Scale averagely constituted $- 2,4 \pm 0,7$. The onset of disease was observed averagely at the age of $55,9 \pm 8,6$ years. The disease duration constituted from 0,5 to 15 years, the average disease duration - $6,4 \pm 4$ years. The akinetic-rigid form of PD was diagnosed in 13 (52%) patients, the rigid-tremor form – in 12 (48%) patients.

According to the analysis of the stabilogram, the plane curve of the amplitude curve of the body fluctuation in the standing position with open eyes characterized the unsteady balance of the body by PD.

There was also discovered a significant dissociation between the clinical manifestation of postural instability and stabilometric indicators representing the state of vertical body balance.

The analysis of the stabilogram depending on the age and PD duration showed significant correlations between the age of patients and the test with OE and between the disease duration and the test with T ($r = -0,4$ and $-0,6$ respectively, $p \leq 0,05$), which corresponds to the literature data. For example, in the work of Yunishchenko N.A. (2006) there is revealed the dependence of the statokinesiogram with the PD duration and the stage according to the Hoehn and Yahr Rating Scale [11]. Thus, at the late PD stage the growth of walking

and postural stability disorders can be connected with the desautomatization of movement programs, progression of regulatory and neurodynamic disorders in the brain.

There was revealed a considerable difference between the stabilometry parameters in patients with PD and persons of the control group (U-test =236,5; $p \leq 0,05$). The average values of tests in patients: OE – 73,8±26; CE – 61,1±27; T – 62,2±23. In the control group: OE 88,9±8,6; CE – 81,1±8,3; T – 75,1±16,9. At the same time, the indexes of relatives of probands were intermediate: OE – 88,8±4,9; CE – 71,8±26,9; M – 65,8±22,9.

In the course of the current study, the patients were not differentiated according to the stages and the form of the disease due to the small sample. Supposedly, by the tremor PD form there are determined more severe disorders to the side of instability of the normal position, while by the akinetic-rigid form – its hyperstability. There should be considered the question of the diagnostic ability of stabilometry for the akinetic-rigid forms of PD, as the slowness and stiffness can predetermine the reduction of speed of the pressure point movement and the reduction of the statokinesiogram area [12]. Thus, in the work of Tretyakova N.A. et al. (2011) there was conducted the differential clinical and stabilometric analysis of various PD phenotypes [13]. By the tremor PD form, there was revealed the dissociation between the clinically expressed postural instability and stabilometric parameters. While in patients with the rigid disease form the obtained data reflect the disorders of statics, which indicates the necessity of further differential approach by the stabilometric analysis in patients with various clinical PD forms.

Conclusions

The method of statistic stabilometry allows to objectivate the disorders of postural functions and to evaluate there state in dynamics. The age and the disease duration significantly worsen the study indexes. By means of the stabilographic method it is possible to determine the disorder of the regulation of motor activity in healthy people included into the PD risk group.

The results obtained in terms of the current study require further research by the bigger volume of sample.

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EPIDEMIOLOGICAL ASPECTS OF GASTRIC AND CARDIAC CANCER MORBIDITY IN ALTAI KRAI

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The epidemiology of stomach cancer and cardia is an urgent problem of modern healthcare and it ranks second (13.5%) in the structure of mortality from cancer in Russia. Stomach cancer ranks fourth (7.9%) among men, and fifth (5.2%) among women. The article presents the epidemiological analysis of the morbidity of stomach cancer in Altai Krai; it provides recommendations for reducing risks and morbidity rates.

Key words: *oncological diseases, stomach cancer, epidemiology of non-infectious diseases.*

Despite the reduction of morbidity, gastric cancer (GC) remains one of the most common diseases in the world. Yearly, there are registered more than 1 million cases. In the overwhelming majority of countries, GC morbidity in men is 2 times higher than in women. The morbidity level varies rather widely [8;9]. Thus, according to the latest IARC edition "Cancer on 5 continents" (Volume 7), it is absolutely evident, that the value of GC morbidity rate is influenced by the character and regime of nutrition. The presence of enough plant food and fruits, animal and vegetable proteins in the food ration considerably decreases the risk of GC. The most demonstrative example is the USA, where during the last 70 years of sensible nutrition promotion the GC morbidity of population has significantly reduced. It should be noted, that a considerable decrease of GC was registered also in migrants from Japan permanently residing in the USA, especially in the second and third generations.

Research objective: to reveal the epidemiological aspects of gastric cancer and cardia morbidity in the territory of Altai Krai.

Materials and methods

The materials for the retrospective epidemiological analysis of gastric cancer and cardia morbidity in the territory of Altai Krai and the Russia Federation included the statistical data of official sources, there was performed the statistical processing of the obtained data.

Russia refers to the countries with high GC morbidity level with more than 37 thousand new cases registered annually [12]. However, there has emerged a trend to the reduction of GC morbidity in Russia. Since 1990 the morbidity has decreased by 21 thousand (35%) and constituted 37,8 thousand (2015) (Figure 1, 2).

In the structure of oncological morbidity among men GC ranks 4th (7,9%), among women – 5th (5,2%), in the structure of mortality – 2nd (13,5%) [1]. In this regard, the problem of GC epidemiology, its early

diagnostics and prevention remain topical.

According to the level of GC mortality in the array of 45 countries Russia holds the 2nd position (in men) and 3rd position (in women). Despite the reduction of morbidity, during the recent 10 years the rate of mortality in the first year even increased, which is connected with the growth of the number of patients with IV stage. In 2015 in Altai Krai the standardized index of GC mortality in men constituted 19,4, in women – 7,5 per 100 000 population, which is somewhat higher than the Russian index (17.9 and 7,3 respectively) [1; 2]. The highest survival rate is registered in Japan – 53%, in other countries it does not exceed 15-20% [5]. The rate of early GC in Japan is also the highest and constitutes the half of all cases, while in Europe, the USA and other countries - not –exceeding 20%. The success of survival improvement in Japan is determined by screening of population and establishment of national cancer programs [14].

During the past decade there has been registered an increase of morbidity of cardio-esophageal cancer and a decrease of antral cancer morbidity, and this trend is most well-marked in European countries, while Japan is dominated by athral cancer [4; 13]. It is supposed, that GC of distal organs is associated with the *Helicobacter pylori* infection (HP), and eradication treatment regimens cause HP migration in the proximal direction leading to the cancerogenic effect in the cardio-esophageal zone.

Researchers pay great attention to the role of HP by the determination of GC causes. After in 1983 B.J. Marshall [15], while studying the biopsy materials of gastric mucosa of patients with ulcer disease, discovered and described a microorganism classified as HP subsequently considered as the leading one in the etiology of chronic nonimmune antral gastritis, the researchers became interested in its influence on GC.

Ye.L. Fischeleva [11] notes in the survey for the role of HP in GC development, that according to the studies conducted in the USA and England, the risk of GC development in the infected

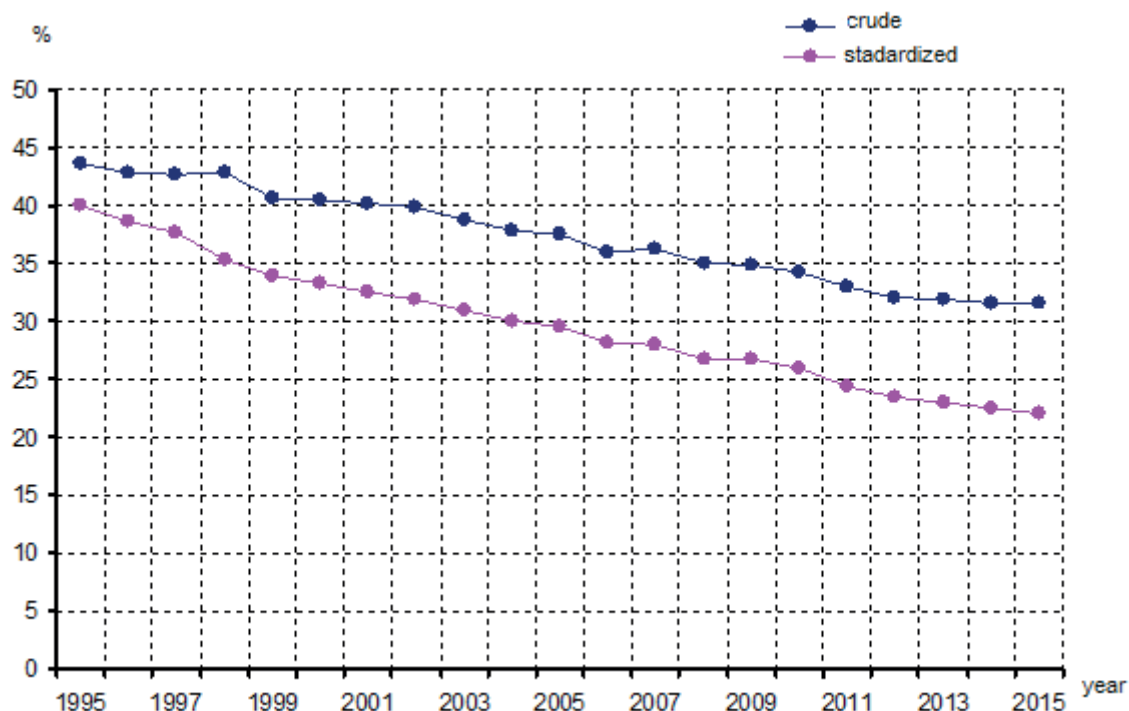


Figure 1. Dynamics of GC morbidity of the Russian population (men)

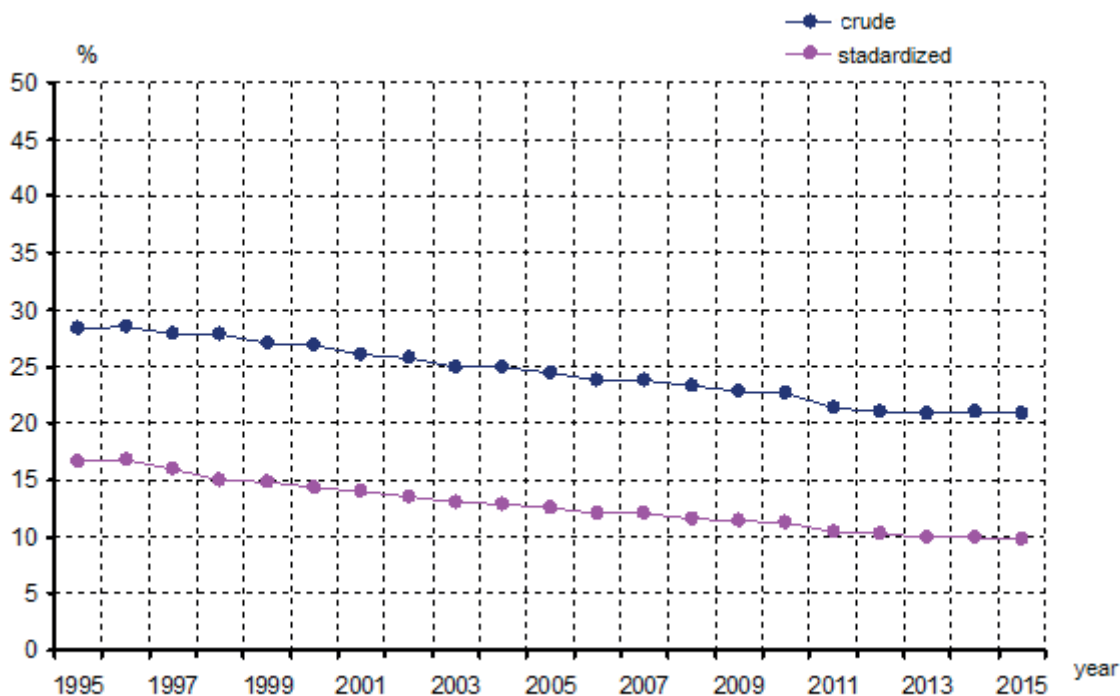


Figure 2. Dynamics of GC morbidity of the Russian population (women)

patients is 3,8 times higher than in the noninfected patients. Prospective researcher performed with an interval of 15 years and more revealed HP infection in 90%, and by ruling out cardiac cancer this percent became even higher. According to our observations, HP bacterization by GC constituted 92%.

In Altai Krai there was also marked the reduction of GC morbidity during recent 20 years, both in men (from 41,9 to 37,7) and in women (from 16,8 to 10,5) per 100 thousand population (Figure 3,4).

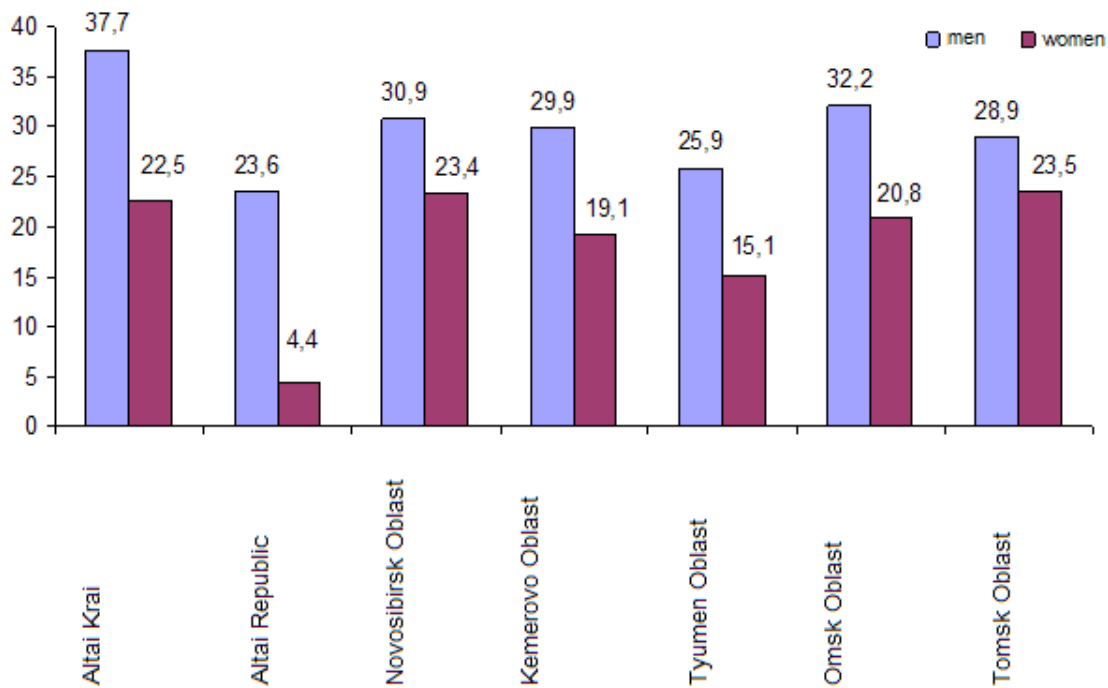


Figure 3.
GC morbidity in the Western-Siberian region ("Crude" index. 2015)

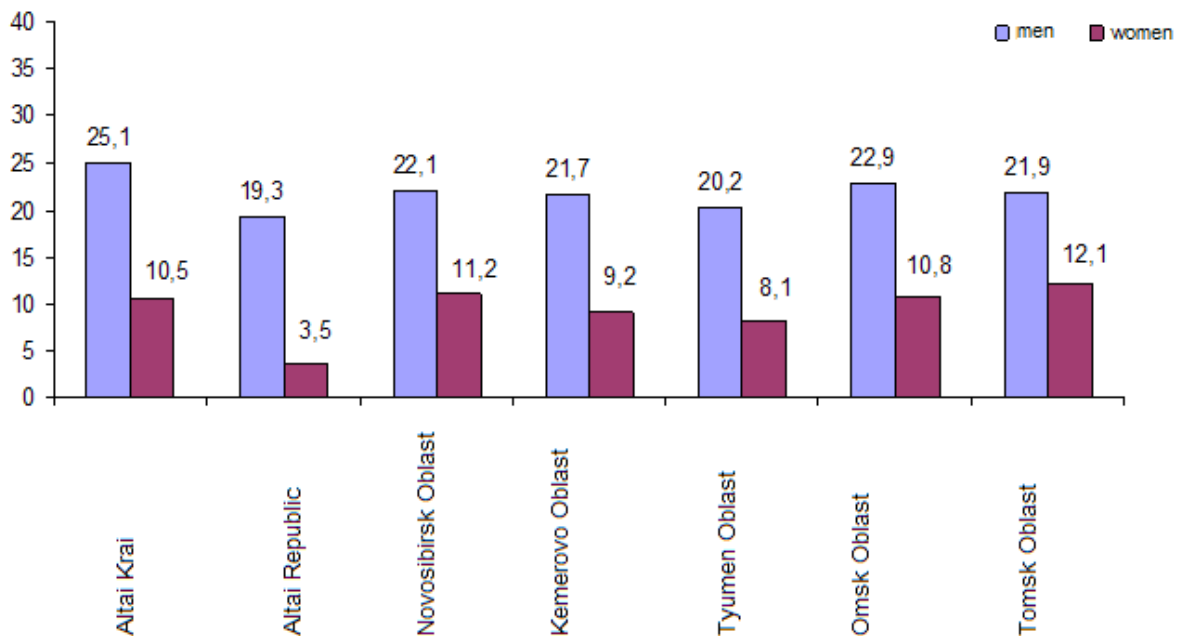


Figure 4.
GC morbidity in the Western-Siberian region (Standardized index. 2015)

In the Western-Siberian region there is observed the territorial inequality of GC extension (Figure 3,4). There is revealed the connection of the disease with the regional specifics, which is determined by the peculiarities of the live environment including natural landscape, anthro-

po-ecological characteristics, presence of rhodonic waters, seismic activity, health levels, population density and migration manifesting itself firstly through the factors of nutrition and stress. Critically important is also the factor of social and natural strain caused by the stress syndrome of population

[9]. GC morbidity in Altai Krai among Western-Siberian regions is higher both in men and women, and is conditioned by such natural factors as natural radon, technogenic pollution by salts of heavy metals, consequences of explosions at Semipalatsinsk test site.

Over the past 20 years in the whole world there has been marked a sharp increase of cardio-esophageal cancer (CEC) against the background of GC morbidity reduction, which makes the problem of treatment of neoplasms of the stated location extremely topical. The rates of growth of this neo-

plasm morbidity exceeded identical rates by other malignant tumors [3; 12] (Figure 5).

The experience of numerous large clinics show, that CEC and cancer of other gastric elements are different diseases. Tumors of the cardio-esophageal zone metastasized not only into abdominal, but often into mediastinal lymph nodes. From the point of prognosis they are more unfavorable than gastric or esophageal cancer. In Altai Krai CEC morbidity over the recent 20 years has grown nearly by 2 times (1994 – 2,1 2015- 3,9) (Figure 5).

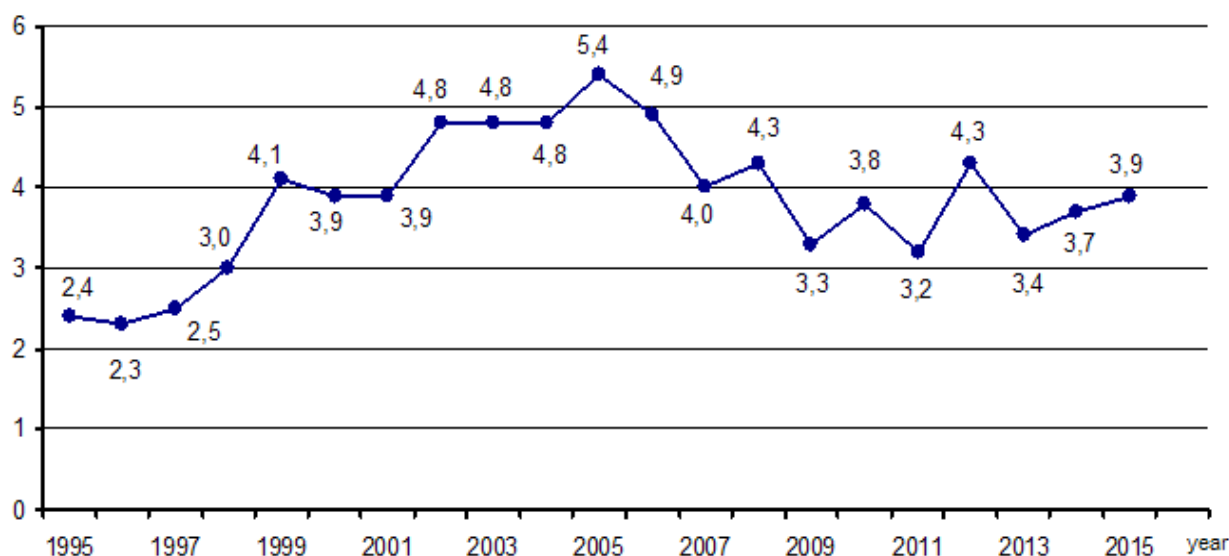


Figure 5. Dynamics of CEC morbidity in Altai Krai (both genders). "Crude" index

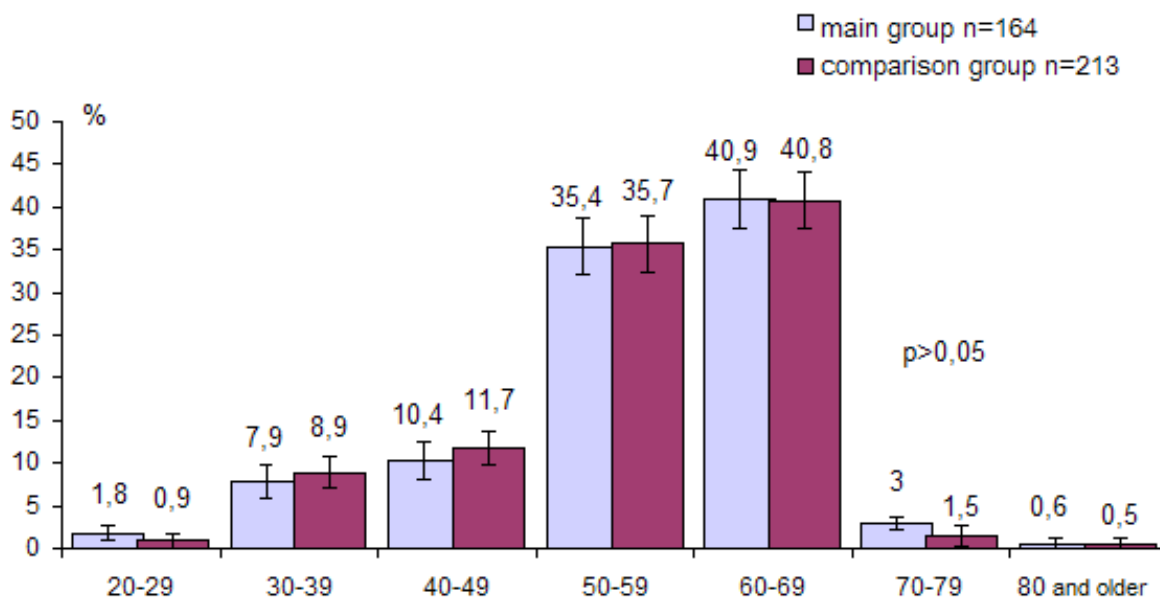


Figure 6. Age characteristics of CEC morbidity in Altai Krai during the past 10 years

The basic contingent of CEC morbidity is accounted for the age group of 50-60 years (76,3%) (Figure 6).

At the joint conference of the International gastric cancer association and the International society for diseases of the esophagus in 2000 the expert committee recommended the classification suggested by J.R.Siewert (1987). It is simple for understanding and practical use. The classification is based on the anatomic center of the tumor with Z-line as the starting point. The classification allows to differentiate the tumors located in the area of esophagogastric junction and to choose the most suitable surgical access.

Treatment of CEC still remains a multifaceted topical problem. Increased attention of the surgeons is focused on the problem of adequate access, degree of surgical intervention, volume of lymph node dissection, reduction of postoperative mortality and improvement of functional consequences of operations on cardio-esophageal cancer. Numerous researches both in the RF and abroad are devoted to the search of adequate methods of surgical treatment and elaboration of effective combined methods.

During the past 20 years in Altai Krai there has been registered 596 cases of CEC morbidity. Men are exposed to this disease nearly 2 times oftener than women (31,4% and 69,6%). CEC morbidity is higher among urban population (54,7%) in comparison with rural population (45,3%).

Table 1

Tumor localization according to gastric elements (2005-2015)

Gastric element	ICD-10	%
Cardia	C16.0	11,6
Gastric fundus	C16.1	0,8
Gastric corpus	C16.2	35,7
Pyloric end of stomach	C16.3	2,2
Pylorus	C16.4	18,4
Lesser curvature	C16.5	4,3
Major curvature	C16.6	1,6
Extensive overall gastric affection	C16.8	4,7
Nonrefinement gastric localization	C16.9	20,7
TOTAL (5498 cases)	C16	100

According to our observations, out of 5498 cases of GC the tumor localization during recent years gradually moves to the upper gastrointestinal due to the conducted treatment described above. Thus, cardio-esophageal cancer constitutes 11,6% (Table 1).

According to J.R. Siewert tumor classification, in our studies tumors were located: I type – in men – 31,4%, in women – 16,8%, II type – 65,9% in men, 79,4% in women, III type – 2,6% in men and 3,8% in women. The frequency of CEC of I type occurrence is determined by Barrett's epithelia metaplasia connected with the character of nutrition (smoking, alcohol abuse).

Table 2

Histological structure of cardio-esophageal tumors (2000-2015)

Code ICD-0-2	Name	Number of cases	%
8140/3	Adenocarcinoma NOS	76	12,8
8140/3	High-grade differentiated adc	126	21,2
8140/3	Moderately differentiated adc	178	29,8
8140/3	Low-grade differentiated adc	165	27,7
8071/3	Squamous cell keratinous carcinoma	14	2,3
8072/3	Squamous cell nonkeratinous carcinoma	9	1,5
8231/3	Carcinoma simplex	4	0,7
8480/3	Mucinous adenocarcinoma	9	1,5
8560/3	Adenosquamous carcinoma	6	1,0
8260/3	Papillary adenocarcinoma	5	0,8
8240/3	Argentaffin carcinoma	4	0,7
TOTAL morphologically verified		596	100%

There were primarily observed different types of adenocarcinoma constituting 92% of tumors. Irrespective of the tumor type there dominate low-grade differentiated varieties. Squamous cell carcinoma constituted 3,8% (Table 2).

Conclusion

Thus, GC and cardiac cancer remains an extremely pressing problem in Russia. In the mortality structure it holds the second position (13,5%). "Early cancer" is diagnosed in 10% of cases, 75% of primary diagnosed gastric cancer are registered at III-

IV stages, 83% of patients by the moment of case definition have metastases into regional lymph nodes. Thus, there are required screening programs for definition of the most common gastric cancer forms, and in modern conditions HC screening should be conducted at least in the groups of background and pre-malignant diseases. In this respect there is needed the popularization of knowledge (including TV, radio, leaflets etc.) about GC among general practitioners and among the population. A special role should be given to therapists, gastroenterologists, endoscopists. An effective measure of GC prevention can be the change of nutrition. Patients with GC should be treated in specialized medical institutions. By family GC there should be carried medical genetic consultation of relatives.

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TWO CASES OF FRACTURES OF THE FIRST RIB IN TEENAGERS

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Stress fractures more often affect bones of lower limbs, but there also occur other localizations: collar bone, first rib, antebrachium etc. The current work presents two cases of stress fractures of the first rib in teenagers.

Key words: stress fracture of the first rib in teenagers.

Stress fractures are quite frequently diagnosed in children and teenagers exposed to constant monotonous physical load (including sports) as a result of bone overload, but not a stroke or trauma.

Reinberg S.A. (1964) outlines a separate issue of first rib fractures, as they possess a number of clinical and radiological peculiarities. Specific fractures of the first rib sometimes occur by an intensive cough, nose blowing, sneezing, primarily, in serious bed patients with large segments of thoracic cavity excluded from respiratory function. The similar mechanism of occurrence of such fracture is observed in pregnant women in late pregnancy or during labor. One of intensive movements causes an immediate sharp localized pain [1].

Vesnina A.G. and Semenov I.I. (2002) describe stress fracture as a genuine lateral fracture of bone diaphysis without displacement occurring not as a result of a single trauma, but due to long-term bone overload. Such fractures of II-II metatarsal bones after continuous walking are well studied and called "march" fractures.

The bones of lower limbs suffer most often: cannon bones, metatarsal bones etc., but there occur other localizations: collar bone, first rib, antebrachi-

um etc. Clinically, there are registered moderate pains, including slight swelling and functional restrain of the limb.

X-ray picture is quite typical: thin, lateral, well defined fracture line (by current fracture) combined with peristal and central callus (at the stage of callus formation) [2].

1. Patient, 14 years old. The check photofluorographic examination revealed changes in the first rib on the right. No complaints. Two months ago, the patient had felt pain in the neck during break dancing at a school disco. The patient received house treatment with pain relievers and ointments.

2. Patient, 15 years old. By carrying bags with potatoes and loading them into the truck, there appeared pains in the shoulder. No medical aid was requested.

The data of multispiral computed tomography: Both patients had an identical picture: in the middle region of the first rib on the right there was observed a lateral fracture line with callous adjoining surface and marginal bone proliferations due to periosteal changes. No displacement or deformations of the rib axis were observed.

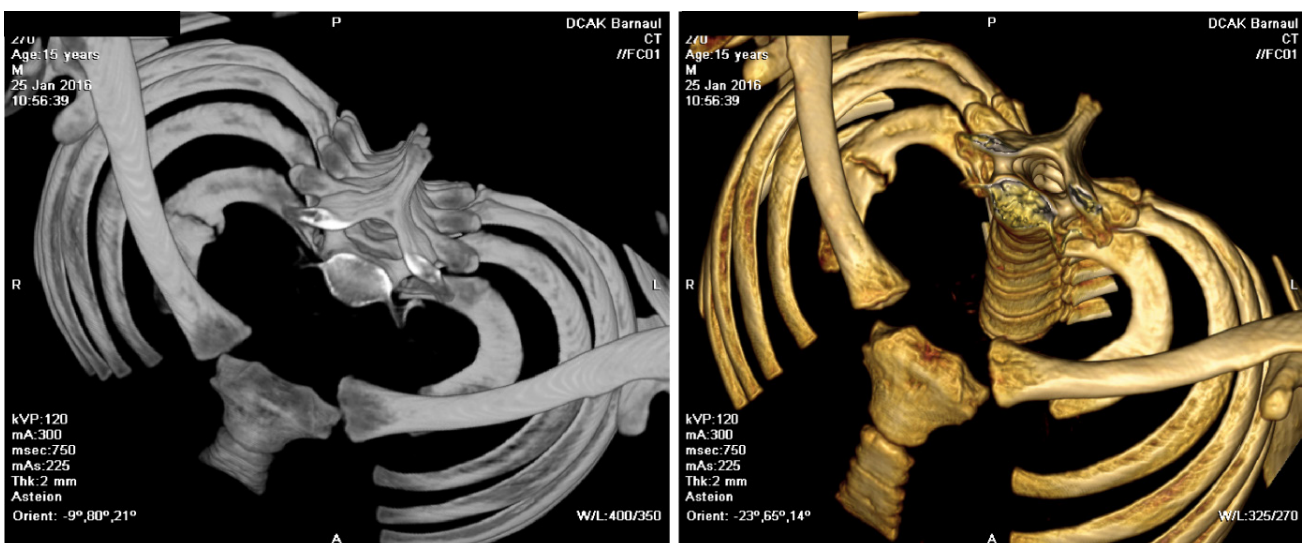


Figure 1.
Multispiral computed tomography of the chest of a 14-year-old patient

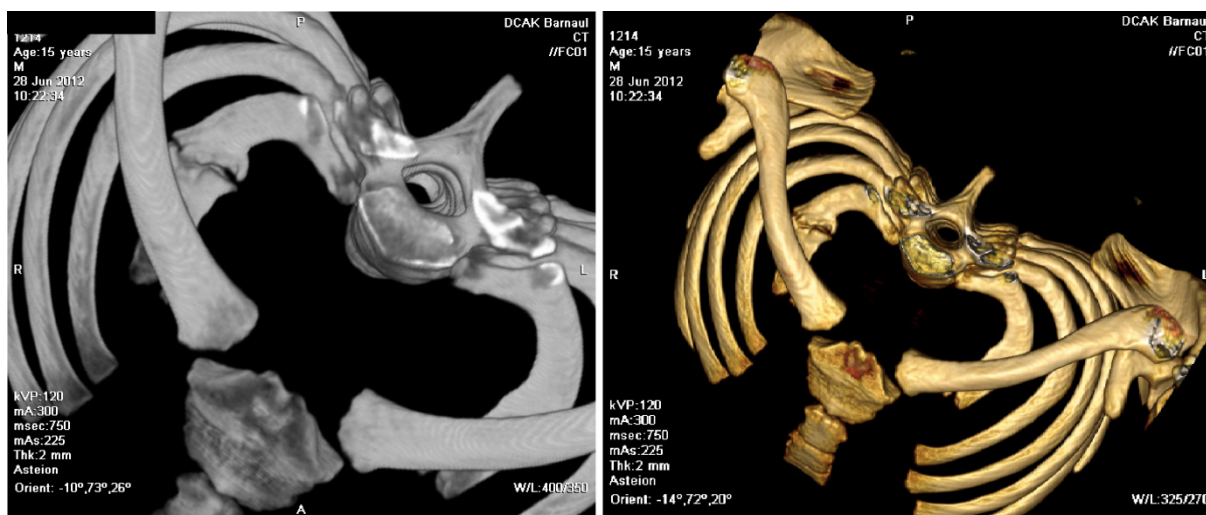


Figure 2.
Multispiral computed tomography of the chest of a 15-year-old patient

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PRESEPSIN AND PROCALCITONIN – MARKERS OF SEPSIS AND SEVERE PNEUMONIA

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Markers of inflammation procalcitonin (PCT), presepsin (PSP) are used against pneumonia, sepsis. The research objective was to study PCT, PSP to improve the diagnosis of severe pneumonia, sepsis. There was totally evaluated 172 patients at the age from 17 to 87. Out of them 118 patients had community-acquired pneumonia (CAP), sepsis, other purulent diseases. These patients were investigated for the level of PCT. PCT was determined quantitatively in ng/ml by the immunofluorescence analyzer miniVIDAS (Biomerye, France). 54 patients with pneumonia, sepsis and other inflammatory diseases have been investigated for the level of the presepsin. Presepsin level was determined quantitatively in pg/ml by means of chemiluminescent immunoassay analyzer Pathfast (Mitsubishi Chemical Medicine Corporation, Japan). All patients had received antibacterial therapy in other health care organizations before entering the hospital. Results: 1. PCT research. PCT level of patients with community-acquired pneumonia (CAP) ($2,1 \pm 0,98$, $n = 10$; $\pm m$) and pneumogenic sepsis ($3,7 \pm 2,01$, $n = 12$) upon admission did not differ ($p > 0.05$). PCT of patients with severe CAP ($3,4 \pm 1,82$, $n = 5$) did not differ from the PCT by pneumogenic sepsis without renal dysfunction ($2,6 \pm 1,52$, $n = 5$, $p > 0.05$). 2. PSP research. There were revealed differences between PSP level by severe pneumonia ($642,0 \pm 140,59$, $n = 10$) and sepsis of patients without renal dysfunction ($1412,5 \pm 180,27$, $n = 8$, $p < 0.05$).

Key words: procalcitonin, presepsin, pneumonia, sepsis.

Biological markers, as indicators of biological and pathobiological processes, have been used since early 1990s of the past century [1]. The biological markers by pneumonia and sepsis are procalcitonin (PCT), presepsin (PSP), IL-6, C-reactive protein, leucocytes [2,3].

PCT is used to determine the bacterial nature of a respiratory disease for sepsis diagnostics [1]. PCT presents a prohormone – predecessor of calcitonin [4]. PCT is primarily generated in C-cells of thyroid gland and neuroendocrine lung cells. The stimulatory effect on PCT production is caused by lipopolysaccharide of the bacterial wall. By severe infection the level of PCT increases quite rapidly and preserves for a long time, which makes it a specific sepsis marker. PCT is used in clinical practice for diagnostics and control of the antibacterial therapy (ABT) effectiveness by the treatment of community-acquired pneumonia (CAP) and sepsis.

The American Medical Association had suggested the algorithms of ABT conduction in patients with infections of lower respiratory tracts considering the concentration of PCT and its interrelation by septicemic conditions [5]. The influence of vasoactive drugs, pain killers, anticoagulants or diuretic agents on the change of PCT was not revealed. The reduction of PCT concentration during several days indicated the efficiency of the therapy (surgical, antibacterial).

PSP – is a new biomarker of bacterial and fungal systemic infections [2]. A key role in PSP production is played by activation of macrophages/monocytes,

on the surface of which there is situated membrane receptor protein mCD14. This protein-receptor identifies the signal of presence of infectious bacteria and switches the system of nonspecific immunity and the inflammatory process connected with it. After the activation of macrophages, mCD14 detaches from the membrane, enters the circulation and becomes soluble sCD14. Further, there occurs the activation of phagocytosis by means of lysosomal proteinases. Proteinases split sCD14 forming sCD14-ST (PSP).

PSP possesses a number of advantages in comparison with the other anti-inflammatory markers: 1) early rise; 2) precise reflection of severity and dynamics of sepsis; 3) prognosis of outcomes; 4) prognosis of sepsis recurrence.

Objective: to study the markers of inflammation to improve the effectiveness of diagnosis of severe pneumonia and sepsis. For this purpose there was: 1) determined the level of PCT in patients with community-acquired pneumonia, sepsis with prior ABT; 2) determined the level of PSP in patients with pneumonia, sepsis with prior ABT.

Materials and methods

There were totally examined 172 patients at the age from 17 to 87 years. Out of them 118 patients were investigated for the level of PCT. These patients were under medical treatment in the pulmonary department, surgery infection department, resuscitation and intensive care department of FSBHI “Regional Clinical Hospital” for the period from 2010 to 2014.

The age of patients – from 19 to 87 years, the average age - $52,6 \pm 15,9$ ($\bar{X} \pm m$). Among them 71 (60,2%) men, 47 (39,8%) women. The patients were divided into 4 groups. The 1st group consisted of patients with CAP (n=19, 16,1%), 2nd group – patients with pneumogenic sepsis (n=12, 10,2%), 3rd group – patients with abdominal sepsis (n=57, 47,3%), 4th group – other purulent diseases (pancreonecrosis, phlegmonous cholecystitis, phlegmon of anterior abdominal wall, acute suppurative mastitis) (n=30, 25,4%).

In 54 patients there was stated the level of PSP. The patients were under medical treatment in the pulmonary department, surgery infection department, resuscitation and intensive care department of FSBHI “Regional Clinical Hospital” for the period from 2010 to 2014. The age of patients – from 17 to 77 years, the average age - $54,4 \pm 2,44$ ($X \pm m$). Among them 34 (63,2 %), men, 20 (36,8%) women. The 1st group consisted of patients with pneumonia (n =16, 29,6 %), 2nd group – patients with pneumogenic sepsis (n = 14, 25,9 %), 3rd group – patients with abdominal sepsis (n = 16, 29,6 %), 4th group – other purulent diseases (purulent pyelonephritis, phlegmonous appendicitis, cholecystitis, etc.) (n = 8, 14,9 %).

The PCT level was was determined quantitatively by the immunofluorescence analyzer mini-VIDAS (Biomerye, France). The results are presented in nanograms per milliliter (ng/ml). PCT was determined upon admission, in 5 and more days.

The PSP level was determined quantitatively by means of chemiluminescent immunoassay ana-

lyzer Pathfast (Mitsubishi Chemical Medience Corporation, Japan). The results are presented in picograms per milliliter (pg/ml). PSP was determined upon admission.

The management of patients was performed in accordance with current clinical recommendations and standards. The antibiotic treatment included: penicillins (ampicillin, ampicillin/ sulbactam, amoxicillin/clavulanate), cephalosporins (cefazoline, ceftriaxone, cefotaxime, ceftazidime, cefoperazone, cefoperazone/ sulbactam, cefepime, ceftaroline), carbapenems (meropenem, ertapenem, imipenem/cilastatin); aminoglycosides (amikacin, gentamycin); macrolides (azithromycin); glycopeptides (vancomycin); oxazolidinones (linezolid); other antibiotics (tigecycline); nitroimidazole (metronidazole); sulfanilamides and trimethoprim (co-trimoxazole); quinolones (levofloxacin, moxifloxacin, ciprofloxacin); antimycotics (f luconazole); antiviral agents (oseltamivir, acyclovir). All patients had been exposed to ABT in other healthcare organizations before admission to FSBHI “Regional Clinical Hospital”.

The statistical data processing was conducted by means of Microsoft Excel program package. Statistically significant differences were determined by means of Student t-test.

Results and discussion

1. Results of PCT examination

The level of PCT in patients with CAP, pneumogenic sepsis and abdominal sepsis is presented in Table 1.

Table 1

PCT in patients with CAP, pneumogenic and abdominal sepsis

Index	Patients with CAP (1)	Patients with pneumogenic sepsis (2)	Patients with abdominal sepsis (3)	p		
	$\bar{X} \pm m$	$\bar{X} \pm m$	$\bar{X} \pm m$	1-2	1-3	2-3
PCT upon admission	2,1±0,98 n=10	3,7±2,01 n=12	18,4±6,31 n=27	>0,05	<0,05	<0,05
PCT in 5 days and later	0,2±0,04 n=9	-	13,1±6,65 n=30	-	<0,05	-
PCT in all patients	1,2±0,55 n=19	3,7±2,01 n=12	15,6±4,57 n=57	>0,05	<0,05	<0,05

PCT level in patients with CAP and pneumogenic sepsis upon admission did not differ significantly. PCT in patients with CAP upon admission constituted $2,1 \pm 0,98$, n=10, which was lower than the level of PCT in patients with abdominal sepsis - $18,4 \pm 6,31$, n=27 (p<0,05). PCT in patients with pneumogenic sepsis upon admission - $3,7 \pm 2,01$, n=12, which was lower than in patients with abdominal sepsis $18,4 \pm 6,31$, n=27 (p<0,05).

PCT in patients with CAP in 5 days and later constituted $0,2 \pm 0,04$, n=9, which was lower than

in patients with abdominal sepsis - $13,1 \pm 6,65$, n=30 (p<0,05).

PCT level in patients with CAP and pneumogenic sepsis in the general group did not differ. PCT in the general group by CAP was $1,2 \pm 0,55$, n=19, which was lower than in patients with abdominal sepsis - $15,6 \pm 4,57$, n=57 (p<0,05). PCT in patients with pneumogenic sepsis in the general group equaled $3,7 \pm 2,01$, n=12, in patients with abdominal sepsis - $15,6 \pm 4,57$, n=57 (p<0,05).

The concentration of PCT upon admission in patients with severe pneumonia constituted $3,4 \pm 1,82$, $n=5$, which did not differ from PCT by pneumogenic sepsis without renal dysfunction - $2,6 \pm 1,52$, $n=8$, ($p>0,05$).

The level of PCT in patients with CAP, pneumogenic sepsis and abdominal sepsis in comparison with the patients with other inflammatory diseases is presented in Table 2.

Table 2

PCT in patients with CAP, pneumogenic and abdominal sepsis in comparison with the patients with other inflammatory diseases

Index	Patients with CAP (1)	Patients with pneumogenic sepsis (2)	Patients with abdominal sepsis (3)	Patients with other inflammatory diseases (4)	p		
	$\bar{X} \pm m$	$\bar{X} \pm m$	$\bar{X} \pm m$	$\bar{X} \pm m$	1-4	2-4	3-4
PCT upon admission	$2,1 \pm 0,98$ $n=10$	$3,7 \pm 2,01$ $n=12$	$18,4 \pm 6,31$ $n=27$	$24,7 \pm 11,63$ $n=21$	$>0,05$	$>0,05$	$>0,05$
PCT in 5 days and later	$0,2 \pm 0,04$ $n=9$	-	$13,1 \pm 6,65$ $n=30$	$3,4 \pm 1,43$ $n=9$	$<0,05$	-	$>0,05$
PCT in all patients	$1,2 \pm 0,55$ $n=19$	$3,7 \pm 2,01$ $n=12$	$15,6 \pm 4,57$ $n=57$	$17,7 \pm 8,04$ $n=30$	$<0,05$	$>0,05$	$>0,05$

The level of PCT in patients with CAP, pneumogenic sepsis and abdominal sepsis in comparison with the patients with other inflammatory diseases did not differ significantly.

PCT in patients with CAP in 5 days and later constituted $0,2 \pm 0,04$, $n=9$, which was lower than in patients with abdominal sepsis - $3,4 \pm 1,43$, $n=9$, ($p<0,05$). The level of PCT in 5 days since admission and later in patients with abdominal sepsis

and other inflammatory diseases did not differ significantly.

PCT in patients with CAP in the general group equaled $1,2 \pm 0,55$, $n=19$, which was lower than in patients with other inflammatory diseases - $17,7 \pm 8,04$, $n=30$, ($p<0,05$).

2. Results of PSP examination

The level of PSP in patients with sepsis and other inflammatory diseases is presented in Table 3.

Table 3

PSP in patients with pneumogenic, abdominal sepsis and other inflammatory diseases

Index	Patients with pneumogenic sepsis (1)	Patients with abdominal sepsis (2)	Patients with other inflammatory diseases (3)	p		
	$\bar{X} \pm m$	$\bar{X} \pm m$	$\bar{X} \pm m$	1-2	1-3	2-3
PSP upon admission	$3083,8 \pm 598,10$ $n=14$	$2867,4 \pm 503,64$ $n=16$	$873 \pm 132,92$ $n=8$	$>0,05$	$<0,05$	$<0,05$

The level of PSP upon admission by pneumogenic sepsis in the general group constituted $3083,8 \pm 598,10$ pg/ml, $n=14$, by abdominal sepsis in the general group - $2867,4 \pm 503,64$ pg/ml, $n=16$ ($p>0,05$). In patient with other inflammatory diseases

PSP was $873 \pm 132,92$ pg/ml, $n=8$, which differed from PSP by pneumogenic and abdominal sepsis ($p<0,05$).

The level of PSP by pneumonia and pneumogenic sepsis is presented in Table 4.

Table 4

PSP in patients with pneumonia and pneumogenic sepsis

Index	Patients with severe pneumonia (1)	Patients with pneumogenic sepsis without renal dysfunction (2)	Patients with severe pneumogenic sepsis with renal dysfunction (3)	p	
	$\bar{X} \pm m$	$\bar{X} \pm m$	$\bar{X} \pm m$	1-2	2-3
PSP	$642,0 \pm 140,59$ $n=10$	$1412,5 \pm 180,27$ $n=8$	$5434,5 \pm 881,41$ $n=4$	$<0,05$	$<0,05$

The level of PSP by pneumogenic sepsis by exclusion of patients with severe sepsis, chronic kidney disease and acute renal dysfunction, exposed to hemodialysis, constituted $1412,5 \pm 180,27$ pg/ml, $n=8$, in comparison with PSP of patients with pneumogenic sepsis and renal dysfunction, exposed to hemodialysis - $5434,5 \pm 881,41$ pg/ml, $n=4$, ($p < 0,05$).

The PSP concentration in one patient with abdominal sepsis constituted 3150 pg/ml. The level of PSP in patients with severe abdominal sepsis - $2601,2 \pm 650,85$ pg/ml, $n=12$. Patients with abdominal sepsis did not receive hemodialysis.

The level of PSP in patients with severe pneumonia was $642,0 \pm 140,59$ pg/ml, $n=10$, while in patients with light form of pneumonia it constituted $231,3 \pm 54,26$ pg/ml, $n=6$, ($p < 0,05$).

PSP in patients with severe pneumonia constituted $642,0 \pm 140,59$ pg/ml, $n=10$, which was lower than in patients with pneumogenic sepsis without renal dysfunction - $1412,5 \pm 180,27$ pg/ml, $n=8$, $p < 0,05$.

In current research the level of PCT upon admission in patients with CAP with prior ABT constituted $2,1 \pm 0,98$ ng/ml. In the work of M. Bafadhel et al., it is shown, that by CAP in primary health care, the level of PCT was 1,27 ng/ml [6].

In this study, we determined the PCT values in patients with pneumogenic, abdominal sepsis and other inflammatory diseases with prior ABT. The literature sources concerning this issue are limited.

The differences between PCT by CAP and pneumogenic sepsis in patients with prior ABT were not found in our study. The level of PCT by CAP was lower, than by abdominal sepsis and other inflammatory diseases. The difference between PCT by abdominal sepsis and other inflammatory diseases in patients with prior ABT was not revealed.

The determination of PCT level is used to improve ABT prescription. According to literature, the implementation of "biomarker-oriented" therapy reduces the terms of ABT and the number of antibiotic associated adverse events compared to the standard therapy by CAP [4]. The use of procalcitonin-oriented therapy did not effect mortality and hospital admission to the resuscitation and intensive care department by infections of lower respiratory tracts.

In terms of the study, the level of PSP in patients with pneumogenic sepsis constituted $1412,5 \pm 180,27$ pg/ml ($n=8$). In patients with severe abdominal sepsis - $2601,2 \pm 650,85$ pg/ml, $n=12$. Our data differ slightly from the literature sources. The recommendations on patient management by suspected sepsis include the following values of PSP (pg/ml): < 200 – very low risk of sepsis development; $200-300$ – low risk of sepsis; $500-1000$ – sepsis; ≥ 1000 – severe sepsis, septic shock [2]. In the study by M. Behnes et al., the diagnostic levels of PSP were

the following: ≥ 530 pg/ml by sepsis; ≥ 600 pg/ml by severe sepsis. In the research, presepsin is considered significant by determination of the severity of sepsis. Consequently, by diagnostics and determination of the severity of sepsis, it is reasonable to consider the recommended values of PSP.

The results of our study showed, that PSP in patients with pneumogenic sepsis exposed to hemodialysis constituted $5434,5 \pm 881,41$ pg/ml ($n=4$), which does not contradict the literature data. PSP is filtrated in renal glomerules, reabsorbed and metabolized in proximal convoluted tubules. There exist data on the increase of PSP concentration in patients with renal dysfunction even by lack of infection [7]. The PSP concentration in patients with terminal renal insufficiency before kidney transplantation was 1252 ± 451 pg/ml. After the surgery the level of PSP reduced. These data indicate, that kidneys play an important role in presepsin clearance.

The level of PSP by mild and severe forms of pneumonia in our research corresponds to the literature data [2].

We revealed the difference between PSP by severe pneumonia and sepsis in patients without renal dysfunction, while the concentration of PCT by severe pneumonia and sepsis did not differ. Thus, PSP reflects the severity of infectious disorder more precisely, than PCT, which does not contradict literature [2].

Conclusion

1. PCT level in patients with prior CAP ($2,1 \pm 0,98$ ng/ml) and pneumogenic sepsis ($3,7 \pm 2,01$ ng/ml) did not differ significantly. These data indicate an extremely severe course of CAP in examined patients.

2. It is reasonable to consider the level of PCT by managements of patients with CAP, sepsis and other inflammatory diseases with prior ABT.

3. There was revealed the difference of PSP level by severe pneumonia ($642,0 \pm 140,59$ pg/ml) and sepsis in patients without renal dysfunction ($1412,5 \pm 180,27$ pg/ml), the level of PCT by severe pneumonia and sepsis did not differ significantly. Thus, PSP reflects the severity of infection more precisely, than PCT. The implementation of the new PSP marker is reasonable by diagnostics and determination of the severity of sepsis.

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REQUIREMENTS FOR PUBLICATION IN THE «BULLETIN OF MEDICAL SCIENCE» JOURNAL

Journal "Bulletin of Medical Science" publishes original researches, case reports, scientific reviews, discussions, sponsored articles and advertisements. All journal sections focus on medical subjects.

The following requirements for publication in the «Bulletin of Medical Science» Journal were developed according to the uniform requirements, stated by the International Committee of Medical Journal Editors (ICMJE) in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication".

MAIN REQUIREMENTS:

1. The article must be followed by official referral of the organization where the work has been done, expert report and scientific supervisor's signature.

2. The article must be published on white paper sheets, A-4 size, on one side of the paper sheet, field width – 2,5-3 cm. 2 copies of the article should be sent to the editorial office.

3. Write initials and surnames of all the authors, the title of the article, the organization where the article has been written at the top of the first page. The signatures of all the authors are required at the end of the article. On a separate page there must be written full names of all authors of the article, and also the address, contact numbers, E-mail of one of the authors for the contact with editorial staff.

4. Article length – 12-18 thousand spaced characters. The number of pictures and tables in accordance with article length. The data presented in the tables must not duplicate the data of the figures and the text, and vice versa.

5. The article must include an abstract in the Russian and English languages. Each of them must be typed on a separate page. Abstract length – 0,5 of a page. At the beginning of an abstract there should be initials and surnames of all the authors and the title of the article. As a new paragraph write 3-5 key words at the end of an abstract.

6. The article must be well-edited by the author. The content of the article must be easy to understand, without long introductions and repetitions. International System of Units (SI) must be used. If you used the apparatus with other units, then all of them must be converted into SI system. Conversion factor or computer program used for the conversion must be mentioned in the section "Materials and methods".

7. Only generally accepted abbreviations are allowed. Firstly, the term must be fully mentioned, then abbreviated. Use only capital letters in abbreviations.

8. Special terms should be given in Russian transcription. Chemical formulas and doses are visaed by the author. Mathematic formulas must be prepared specialized mathematical computer programs or formula editors of "Equation" type.

8. The pictures must be clear, photos – contrasting. On the back of each illustration write the first and the last name of the first author, first two words from the title of the article, the number of the picture; mark the up and down of the picture by the words "up" and "down" in appropriate places. All this information must be written with an ordinary pencil without pressing. Picture captions must be given on a separate page together with the author's surname and the title of the article, the number of the picture, with the explanation of the meaning of all curved lines, letters, numbers and other symbolic representations.

10. The tables must be demonstrable, have the title, sequence number; the headings must be relevant

to the content of columns. Each table should have a reference in the article.

11. The article with original research should have the following parts: 1. "Introduction", 2 "The Purpose of the Research", 3. "Materials and Methods"; 4 "Results"; 5. "Discussion", 6. "Conclusion". In the part "Materials and Methods" there should be given a detailed description of the methodology of the research, the equipment used in the research, the number and characteristics of patients. The principle for the dividing of patients into groups and the design of the research must be compulsory given. This part must contain comprehensive information for further reference to these results by other scientists, for comparing with the results of analogous works and for the possibility of including the data of the article into meta-analysis. At the end of the part "Materials and Methods" there should be a smaller part "Data Processing". The full list of all used statistical methods of analysis and criteria of hypothesis testing must be given. It is not allowed to write "standard statistical methods were used" without their specific indications. It is compulsory to mention the accepted in the research the critical level of significance "p" (e.g. "The critical level of significance in case of statistical hypothesis testing in this research is 0,05"). In each specific case there must be given the actual value of the reached level of significance "p" for the used statistical criterion (not just "p<0,05" or "p>0,05"). Besides, it is necessary to state specific indications of the received statistical criteria (e.g. criterion "Chi-square" = 12,3 (number of degrees of freedom df = 2, p=0,0001). It is compulsory to give the definition for all used statistical terms, abbreviations and symbolic notations (e.g. M – sample mean, m (SEM) – error in mean, STD – sampling standard deviation, p- reached level of significance). In case of combinations like M±m it is necessary to give the meaning of each symbol, and also sample volume (n). If the used statistical criteria have limitations in their usage, specify how these limitations were checked and what the results of these checks are (e.g. in case of using parametric methods it is necessary to show how the normality fact of sample distribution was proved). Avoid non-specific usage of terms which have a few meanings: (e.g. there are a few variants of correlation coefficient: Pearson, Spearman and others). Average quantities should not be given more precisely than for one decimal mark in comparison with base data, mean-square deviation and error in mean – for one more mark precisely.

12. The literature list must be typed on a separate page, each source from the new line with sequence number. The numeration must be done according to the order of citation of the source in the article. The author is responsible for the correctness of the literature list data. The names of foreign authors are given in authentic transcription.

13. The text should be duplicated in the electronic form in WORD (the text is typed without paragraph breaks, hyphenation) and be sent on a CD and (or) by e-mail with the note "For the Bulletin of Medical Science". Each picture\photo should be sent as a separate .jpeg file, resolution not less than 300 dpi. The tables and diagrams must be sent in EXCEL, the name of the file must be the same as the name of the basic file. The format of the file with the article should be compatible with MS Word.

14. The editorial board reserves the right to edit the sent articles. The reviews on the articles are sent to the authors upon written request.

15. The articles not following the stated requirements are not reviewed, the sent articles are not returned back.