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Predictors of individual immune responses to adaptogens

O.I. MEL'NYK¹, Z.D. STRUK²

¹*Danylo Halyts'kyi National Medical University, L'viv, Ukraine*

²*Ukrainian Scientific Research Institute of Medicine for Transport, Odesa, Ukraine*

E-mail: omelnyk7@gmail.com

Introduction. Earlier in the experiments in rats [1,2] and in clinical observations [3–5] showed that the immune responses to chronic stress are ambiguous and individual. Adaptogens, in particular balneofactors, are antipodes of stressors [6]. The immune responses to balneotherapy are also ambiguous [7–19] which is a separate manifestation of the multivariate effects of balneological agents on the body [20,21]. Therefore, the **purpose** of this study is to analyze variants of immune responses to balneofactors of Truskavets' spa as natural adaptogens and to determine the possibility of their prediction.

Material and methods. The object of observation were 34 men and 10 women aged 24–70 years old, who came to the Truskavets' spa for the treatment of chronic pyelonephritis combined with cholecystitis in remission. The survey was conducted twice, before and after balneotherapy (drinking bioactive water Naftusya three times a day, ozokerite applications, mineral baths every other day for 7–10 days).

Immune status evaluated on a set of I and II levels recommended by the WHO as described in the manuals [22,23]. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD8, CD22 and CD56 from company «Granum» (Kharkiv) with visualization under light microscope with immersion system. Subpopulation of T cells with receptors high affinity determined by test of “active” rosette formation. The state of humoral immunity judged by the concentration in serum of Circulating Immune Complexes (by polyethylene glycol precipitation method) and Immunoglobulins classes M, G, A as well as in saliva of IgG, IgA, secretory IgA and Lysozyme (ELISA, analyser “Immunochem”, USA).

Parameters of phagocytic function of neutrophils estimated as described by SD.

Douglas and PG Quie [24] with moderately modification by MM Kovbasnyuk [25]. The objects of phagocytosis served daily cultures of *Staphylococcus aureus* (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and *Escherichia coli* (O55 K59) as typical representative of Gram-negative Bacteria. Both cultures obtained from Laboratory of Hydro-Geological Regime-Operational Station JSC “Truskavets'kurort”. Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes – Hamburger's Phagocytic Index PhI), intensity (number of microbes absorbed one phagocytes – Microbial Count MC or Right's Index) and completeness

(percentage of dead microbes – Killing Index KI). On the basis of the recorded partial parameters of Phagocytosis, taking into account the Neutrophils (N) content of 1 L blood, we calculated the integral parameter – Bactericidal Capacity of Neutrophils (BCCN) by the formula [6]:

$$\text{BCCN (10}^9 \text{ Bact/L)} = \text{N (10}^9 \text{/L)} \cdot \text{PhI (\%)} \cdot \text{MC (Bact/Phag)} \cdot \text{KI (\%)} \cdot 10^{-4}$$

In portion of capillary blood we counted up Leukocytogram (LCG) (Eosinophils, Stub and Segmentonuclear Neutrophils, Lymphocytes and Monocytes) and calculated two variants of Adaptation Index as well as two variants of Strain Index by IL Popovych [26,27].

$$\text{Strain Index-1} = [(\text{Eo}/3,5-1)^2 + (\text{SN}/3,5-1)^2 + (\text{Mon}/5,5-1)^2 + (\text{Leu}/6-1)^2]/4$$

$$\text{Strain Index-2} = [(\text{Eo}/2,75-1)^2 + (\text{SN}/4,25-1)^2 + (\text{Mon}/6-1)^2 + (\text{Leu}/5-1)^2]/4$$

We calculated also the Entropy (h) of Immunocytogram (ICG) and Leukocytogram (LCG) using classical CE Shannon’s formula [28-31]:

$$\text{hICG} = -[\text{CD4} \cdot \log_2 \text{CD4} + \text{CD8} \cdot \log_2 \text{CD8} + \text{CD22} \cdot \log_2 \text{CD22} + \text{CD56} \cdot \log_2 \text{CD56}]/\log_2 4$$

$$\text{hLCG} = -[\text{L} \cdot \log_2 \text{L} + \text{M} \cdot \log_2 \text{M} + \text{E} \cdot \log_2 \text{E} + \text{SNN} \cdot \log_2 \text{SNN} + \text{StubN} \cdot \log_2 \text{StubN}]/\log_2 5$$

The condition of microbiota is evaluated on the results of sowing of feces and urine.

Norms are borrowed from the database of the Truskavets’ Scientific School of Balneology [10,25].

Results processed by methods of cluster [32] and discriminant [33] analyses, using the software package «Statistica 5.5».

Results and discussion. In order to evaluate the immune responses on a single scale according recommendation by IL Popovych [2,6] immune variables (V) expressed as Z-scores calculated by formula:

$$Z=(V/N - 1)/C_v, \text{ where}$$

N is Mean of Normal Variable,

C_v is Coefficient its variation.

Eleven key immune parameters were used to calculate the Immune Status Index (ISI) by the formula:

$$\text{ISI}=(\text{BCCN St. aur.}+\text{BCCN E. coli}+\text{CIC}+\text{IgM}+\text{IgG}+\text{IgA}+\text{B}+\text{NK}+\text{Th}+\text{Tc}+\text{Ta})/11.$$

Preliminary analysis has shown that in different patients, individual ISI respond to balneotherapy not only in varying degrees, but even in the opposite way. The next phase was conducted Cluster analysis of ISI before and after balneotherapy. Clustering cohort of persons is realized by iterative k-means method. In this method, the object belongs to the class Euclidean distance to which is minimal. The main principle of the structural approach to the allocation of uniform groups consists in the fact that objects of same class are close but different classes are distant [32].

As a result, four groups of persons were created, significantly different from each other in terms of ISI (Table 1 and Fig. 1).

Table 1.

Average values (Mean±SE) of immune status index (ISI) before and after balneotherapy in members of different clusters

	Cluster	Cluster	Cluster	Cluster
	No.1(2)	No.2(14)	No.3(18)	No.4(10)
ISI before	+0,60±0,50	-0,55±0,05	+0,23±0,06	-0,87±0,13
ISI after	-0,95±0,16	+0,22±0,08	+0,35±0,07	-0,68±0,10

Cluster №3 (40,9% of the sample), whose members are characterized by a stable normal (N) immune status, appeared to be the largest, which is quite expected given the remission phase of the chronic inflammatory process. In

members of cluster №2 (31,8%), the lower boundary level of immunity (N-) was completely normalized (N), indicating a favorable immunotropic effect of balneotherapy.

Fig. 1. Individual immune status indexes (ISI) before (axis X) and after (axis Y) balneotherapy in members of different clusters of immune responses

In members of cluster №4 (22,7%), moderate immunosuppression (S) was reduced but not sufficient. However, in two patients of cluster №1 (4,5%), initially normal immune status (N) was transformed into moderate immunosuppression (S). Therefore, the immunotropic effect of balneotherapy on certain individuals is not effective enough, and in some cases even unfavorable.

In order to determine the possibility of predicting the nature of the immune response to balneotherapy on the basis of the initial parameters we have used discriminant analysis. The forward stepwise program included 20 predictors in the model, including 12 immune **blood** parameters and one **saliva** parameter, 4 **information** parameters, 2 **fecal microbiota** parameters as well as **erythrocyturia** (Tables 2 and 3).

Table 2.

Discriminant Function Analysis Summary
for Variables predicting various Immune responses

Step 20, N of vars in model: 20; Grouping: 4 grps; Wilks' Λ : 0,0012; approx. $F_{(60,6)}=9,15$; $p<10^{-6}$

Variables currently in the model	Wilks' Λ	Partial Λ	F-remove (3,2)	p-level	Tolerance
IgA Serum, g/L	,0016	,711	2,85	,062	,396
Bactericidity vs Staph. aur, 10 ⁹ Bacteria/L	,0016	,720	2,73	,070	,125
Popovych's Leukocyetary Strain Index-1, pts	,0044	,264	19,5	10 ⁻⁵	,029
Lysozyme Saliva, mg/L	,0058	,198	28,3	10 ⁻⁶	,079

Variables currently in the model	Wilks' Λ	Partial Λ	F-remo- ve (3,2)	p- level	Tole- rancy
Microbial Count vs Staph. aur, Bact/ Phagoc.	,0014	,813	1,61	,217	,200
0-Lymphocytes of Blood, %	,0019	,621	4,28	,017	,211
Stub Neutrophiles of Blood, %	,0017	,683	3,24	,043	,409
IgG Serum, g/L	,0025	,468	7,96	,001	,335
E. coli faeces, 10 ⁶ CFU/g	,0015	,748	2,36	,101	,165
Microbial Count vs E. coli, Bacter/ Phagocyte	,0035	,330	14,2	10 ⁻⁴	,047
Bactericidity vs E. coli, 10 ⁹ Bacteria/L	,0023	,511	6,71	,002	,066
Entropy of Immunocytogram	,0017	,688	3,18	,045	,294
Popovych's Leukocytary Adaptation Ind-1, pts	,0016	,742	2,44	,093	,263
CD3 ⁺ T-active Lymphocytes, %	,0020	,564	5,40	,006	,407
Popovych's Leukocytary Strain Index-2, pts	,0019	,621	4,28	,017	,048
Pan-Lymphocytes of Blood, %	,0017	,673	3,40	,037	,222
Erhydrocyturia, lg/L	,0017	,689	3,15	,046	,339
CD8 ⁺ CD3 ⁺ T-cytolytic Lymphocytes, %	,0016	,731	2,58	,081	,416
Lactobacillus faeces, lg CFU/g	,0015	,789	1,87	,166	,189
Phagocytose Index vs Staphylococcus aur, %	,0013	,856	1,18	,342	,268

Table 3.

Summary of Stepwise Analysis for Variables predicting various Immune responses.
The variables are ranked by criterion Lambda

Variables currently in the model	F to enter	p-level	Λ	F- value	p- level
IgA Serum, g/L	12,0	10 ⁻⁵	,527	12,0	10 ⁻⁵
Bactericidity vs Staph. aur, 10 ⁹ Bacteria/L	10,9	10 ⁻⁴	,287	11,3	10 ⁻⁶
Popovych's Leukocytary Strain Index-1, pts	6,3	,001	,192	10,0	10 ⁻⁶
Lysozime Saliva, mg/L	7,2	,001	,121	10,0	10 ⁻⁶
Microbial Count vs Staph. aur, Bact/Phagoc.	6,2	,002	,080	10,0	10 ⁻⁶
0-Lymphocytes of Blood, %	5,2	,005	,055	9,8	10 ⁻⁶
Stub Neutrophiles of Blood, %	4,0	,016	,041	9,5	10 ⁻⁶
IgG Serum, g/L	3,2	,036	,032	9,2	10 ⁻⁶
E. coli faeces, 10 ⁶ CFU/g	3,8	,020	,024	9,1	10 ⁻⁶
Microbial Count vs E. coli, Bacter/Phagocyte	2,8	,059	,019	8,8	10 ⁻⁶
Bactericidity vs E. coli, 10 ⁹ Bacteria/L	3,1	,039	,014	8,8	10 ⁻⁶
Entropy of Immunocytogram	4,0	,017	,010	9,0	10 ⁻⁶
Popovych's Leukocytary Adaptation Ind-1, pts	3,5	,027	,007	9,2	10 ⁻⁶
CD3 ⁺ T-active Lymphocytes, %	4,4	,013	,005	9,6	10 ⁻⁶
Popovych's Leukocytary Strain Index-2, pts	2,4	,093	,004	9,5	10 ⁻⁶
Pan-Lymphocytes of Blood, %	2,9	,057	,003	9,7	10 ⁻⁶
Erhydrocyturia, lg/L	3,0	,049	,002	9,9	10 ⁻⁶
CD8 ⁺ CD3 ⁺ T-cytolytic Lymphocytes, %	1,6	,218	,002	9,6	10 ⁻⁶
Lactobacillus faeces, lg CFU/g	2,0	,146	,001	9,5	10 ⁻⁶
Phagocytose Index vs Staphylococcus aur, %	1,2	,342	,001	9,2	10 ⁻⁶

Next, the 20-dimensional space of discriminant variables transforms into 3-dimensional space of canonical roots, which are a linear combination of dis-

criminant variables. The canonical correlation coefficient is for Root 1 0,983 (Wilks' Λ =0,0012; $\chi^2_{(60)}=210$; $p<10^{-6}$), for Root 2 0,943 (Wilks' Λ =0,0337; $\chi^2_{(38)}=105$; $p<10^{-6}$) and for Root 3 0,834 (Wilks' Λ =0,3039; $\chi^2_{(18)}=37$; $p=0,005$). The major root contains 73,1% of discriminative properties, the second 20,9% and the minor 6,0%.

Table 4 presents standardized (normalized) and raw (actual) coefficients for discriminant variables. The calculation of the discriminant root values for each person as the sum of the products of raw coefficients to the individual values of discriminant variables together with the constant enables the visualization of each patient in the information space of the roots.

Table 4.

Standardized and Raw Coefficients and Constants for predicting Variables

	Standardized			Raw		
	Root 1	Root 2	Root 3	Root 1	Root 2	Root 3
IgA Serum, g/L	,678	-,189	,605	1,719	-,478	1,533
Bactericidity vs Staph. aur, 10 ⁹ Bacteria/L	-1,329	,243	-,840	-,077	,014	-,049
Popovych's Leukocytary Strain Index-1, pts	-5,080	-,276	,554	-15,04	-,818	1,641
Lysozime Saliva, mg/L	3,190	-,633	,147	,589	-,117	,027
Microbial Count vs Staph. aur, Bact/Phagoc.	,578	-,400	,823	,089	-,061	,126
0-Lymphocytes of Blood, %	,482	1,222	,591	,099	,251	,121
Stub Neutrophiles of Blood, %	-,841	,165	-,310	-,819	,160	-,302
IgG Serum, g/L	,823	-,530	-,991	,257	-,166	-,309
E. coli faeces, 10 ⁶ CFU/g	-,023	-,354	-1,426	-,0002	-,0030	-,0121
Microbial Count vs E. coli, Bacter/Phagocyte	-3,515	,783	-1,635	-,494	,110	-,230
Bactericidity vs E. coli, 10 ⁹ Bacteria/L	2,073	-1,719	,992	,096	-,080	,046
Entropy of Immunocytogram	,580	,435	,904	22,14	16,58	34,46
Popovych's Leukocyt Adaptation Ind-1, pts	-,622	-,825	-,063	-1,148	-1,522	-,116
CD3 ⁺ T-active Lymphocytes, %	-,970	-,293	-,349	-,193	-,058	-,069
Popovych's Leukocytary Strain Index-2, pts	2,827	,356	-,236	5,700	,717	-,476
Pan-Lymphocytes of Blood, %	-1,064	,620	-,233	-,167	,097	-,037
Erhydrocyturia, lg/L	-,772	,575	-,262	-2,645	1,971	-,899
CD8 ⁺ CD3 ⁺ T-cytolytic Lymphocytes, %	,799	-,014	-,209	,174	-,003	-,046
Lactobacillus faeces, lg CFU/g	-,751	,302	-,839	-,574	,231	-,641
Phagocytose Index vs Staphylococcus aur, %	-,453	-,231	,646	-,424	-,215	,604
		Constants		-37,96	23,06	-75,10
		Eigenvalues		28,119	8,028	2,291
		Cum. Prop.		,732	,940	1,000

Extreme localization along the axis of the first root (Fig. 2) of members of the N/S cluster reflects their maximally increased Popovych's Strain Index-1, Entropy of Immunocytogram, the Intensity of phagocytosis and Bactericidity of neutrophils against both groups of bacteria, on the one hand, and minimal

Popovych’s Adaptation Index-1, maximum Lysozyme deficiency in saliva and IgG in serum in combination with the minimum for the sample increased levels of IgA in it (table. 5). The members of other clusters do not differ in the totality of the predictors listed (mixed along the axis of the first root). Instead, the members of the N/N cluster are clearly distinguished along the axis of the second root, while the S/S and N-/N clusters are mixed. Delimitation of the latter occurs along the axis of the third root (Fig. 3).

Fig. 2. Individual values of the first and second roots in which condensed the information about predictors of various immune responses

Fig. 3. Individual values of the first and third roots in which condensed the information about predictors of various immune responses

Table 5.

Correlations Variables-Canonical Roots, Means of Roots and predicting Variables for Clusters of immune responses

	Correlations Variables-Roots			N/S (2)	S/S (10)	N-/N (14)	N/N (18)	Norm (30)
Root 1 (73,1%)	R1	R2	R3	-22,8	-0,36	+0,85	+2,07	
Popovych’s Leukocy-tary Strain Index-1, pts	-,129	-,006	,106	0,215	0,141	0,203	0,127	0,067
Bactericidity vs E. coli, 10 ⁹ Bacteria/L	-,109	-,235	,041	154	71	80	99	99
Bactericidity vs Staph. aur, 10 ⁹ Bac-teria/L	-,078	-,222	,095	130	75	85	98	106

	Correlations Variables- Roots			N/S (2)	S/S (10)	N-/N (14)	N/N (18)	Norm (30)
Entropy of Immuno- cytogram	-,054	,017	,158	0,995	0,956	0,970	0,957	0,960
Microbial Count vs E. coli, Bacter/Phago- cyte	-,034	,052	,167	70	64	67	62	55
Microbial Count vs Staph. aur, Bact/ Phagoc.	-,029	,071	,194	66	61	65	60	61,6
Lysozime Saliva, mg/L	,121	,121	,074	154	172	173	169	180
IgG Serum, g/L	,077	-,131	-,272	9,4	14,6	12,2	16,5	12,75
IgA Serum, g/L	,075	-,284	,202	1,20	1,41	1,44	1,48	1,15
Popovych's Leukocyt Adaptation Ind-1, pts	,048	-,126	-,013	0,62	0,84	0,95	1,32	1,70
Root 2 (20,9%)				-2,22	+3,31	+1,76	-2,96	
CD3+ T-active Lym- phocytes, %	-,026	-,099	,024	33,0	27,0	28,1	30,0	30,0
Phagocytose Index vs Staphylococcus aur, %	-,001	-,090	,036	99,0	98,3	98,6	99,0	98,3
CD8+CD3+ T-cytolytic Lymphocytes, %	-,018	-,077	-,006	25,5	21,8	22,1	23,8	23,5
0-Lymphocytes of Blood, %	,041	,242	-,077	-4,3	7,6	4,6	0,1	0
Pan-Lymphocytes of Blood, %	-,046	,209	-,144	37,3	40,3	34,3	29,7	32,0
Root 3 (6,0%)				+0,33	-1,99	+1,88	-0,39	
Lactobacillus faeces, lg CFU/g	-,039	-,056	-,239	7,04	6,21	5,05	6,04	8,10
E. coli faeces, 10 ⁶ CFU/g	-,036	,047	-,236	269	268	147	178	455
Stub Neutrophiles of Blood, %	,005	-,128	-,209	2,63	2,51	1,89	3,00	4,25
Popovych's Leukocy- tary Strain Index-2, pts	-,017	,026	,156	0,261	0,199	0,302	0,179	0,065
Erhydrocyturia, lg/L	-,004	,081	,088	3,00	3,07	3,13	2,96	2,70

In general, predictors of all four clusters of immune responses on the planes of the discriminant roots are quite clearly delineated, which is documented by calculating the Mahalanobis distances (Table 6).

Table 6.

Squared Mahalanobis Distances between Clusters,
F-values (df=20,2) and p-levels

Clusters	N/N	S/S	N/S	N-/N
N/N	0	53	679	32
S/S	8,1 10 ⁻⁵	0	592	21
N/S	16,8 10 ⁻⁶	14,0 10 ⁻⁶	0	634
N-/N	6,2 10 ⁻⁴	2,9 0,010	15,4 10 ⁻⁶	0

Predicting the nature of the immune response is realized with the help of classifying functions (Table 7). These functions are special linear combinations that maximize differences between groups and minimize dispersion within groups. An object belongs to a group with the maximum value of a function calculated by summing the products of the values of the variables by the coefficients of the classifying functions plus the constant.

Table 7.

Coefficients and Constants for Classification Functions
of Clusters of Immune responses

Clusters	N/N	S/S	N/S	N-N
Variables	p=,409	p=,227	p=,045	p=,318
IgA Serum, g/L	-22,98	-32,60	-64,91	-23,85
Bactericidity vs Staph. aur, 10⁹ Bacteria/L	-6,20	-5,85	-4,31	-6,15
Popovych's Leukocytary Strain Index-1, pts	-150,0	-121,20	224,1	-131,9
Lysozyme Saliva, mg/L	37,15	34,94	22,46	35,95
Microbial Count vs Staph. aur, Bact/ Phagoc.	5,39	4,59	3,24	5,28
0-Lymphocytes of Blood, %	18,85	19,99	16,67	20,19
Stub Neutrophiles of Blood, %	-36,24	-32,77	-16,01	-35,18
IgG Serum, g/L	-14,60	-15,77	-21,33	-16,40
E. coli faeces, 10⁶ CFU/g	-1,64	-1,64	-1,64	-1,68
Microbial Count vs E. coli, Bacter/ Phagocyte	-58,11	-55,86	-45,92	-57,52
Bactericidity vs E. coli, 10⁹ Bacteria/L	9,73	8,93	7,32	9,34
Entropy of Immunocytogram	6136,8	6132,2	5624,3	6266,5
Popovych's Leukocytary Adaptation Ind-1, pts	-93,66	-100,2	-66,37	-99,72
CD3⁺ T-active Lymphocytes, %	-15,05	-14,83	-10,34	-15,25
Popovych's Leukocytary Strain Index-2, pts	-57,27	-65,86	-198,6	-61,87
Pan-Lymphocytes of Blood, %	-15,43	-14,36	-11,24	-14,85
Erthyrocyturia, lg/L	-492,89	-472,6	-426,3	-482,3
CD8⁺CD3⁺ T-cytolytic Lymphocytes, %	-1,82	-2,19	-6,17	-2,15
Lactobacillus faeces, lg CFU/g	-127,0	-123,1	-113,0	-126,6
Phagocytose Index vs Staphylococcus aur, %	271,12	269,8	281,9	272,0
Constants	-16014,4	-15659,3	-15366,2	-16027,0

We can retrospectively recognize members of three clusters unmistakably, and only the cluster S/S is with one error. This means that, with the help of predictors and classification functions, the identity of a particular person to one or another cluster of immune responses is almost unmistakable.

Conclusion. Four variants of the immune responses of patients with chronic inflammatory process to adaptogenic balneotherapy have been identified. In 40,9% of patients, initially normal immune status did not change significantly. In 31,8%, the lower boundary level of immunity is completely normalized. In 22,7% moderate immunosuppression is reduced, but not up to normal. However, in 4,5% of people, initially normal level of immunity are transformed into moderate immunosuppression. All four variants of immune responses are virtually unmistakably predicted by a set of 20 predictors, which allows us to make adjustments to balneotherapy in advance.

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants. For all authors any conflict of interests is absent.

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RESEARCH ARTICLE

Predictors of individual immune responses to adaptogens

O.I. MEL'NYK¹, Z.D. STRUK²

¹*Danylo Halyts'kyi National Medical University, L'viv, Ukraine*

²*Ukrainian Scientific Research Institute of Medicine for Transport, Odesa, Ukraine*

E-mail: omelnyk7@gmail.com

Introduction. Earlier in the experiments in rats and in clinical observations showed that the immune responses to chronic stress are ambiguous and individual. Adaptogens, in particular balneofactors, are antipodes of stressors. The immune responses to balneotherapy are also ambiguous. Therefore, the **purpose** of this study is to analyze variants of immune responses to balneofactors of Truskavets' spa as natural adaptogens and to determine the possibility of their prediction. **Material and methods.** The object of observation were 34 men and 10 women aged 24-70 years old, who came to the Truskavets' spa for the treatment of chronic pyelonephritis combined with cholecystitis in remission. The survey was conducted twice, before and after balneotherapy (drinking bioactive water Naftusya three times a day, ozokerite applications, mineral baths every other day for 7-10 days). Immune status evaluated on a set of I and II levels recommended by the WHO as described in the manuals. In portion of capillary blood we counted up Leukocytogram and calculated two variants of Adaptation Index as well as two variants of Strain Index by IL Popovych. We calculated also the Entropy of Immunocytogram and Leukocytogram. The condition of microbiota is evaluated on the results of sowing of feces and urine. **Results.** Four variants of the immune responses to adaptogenic balneotherapy have been identified. In 40,9% of patients, initially normal immune status did not change significantly. In 31,8%, the lower boundary level of immunity is completely normalized. In 22,7% moderate immunosuppression is reduced, but not up to normal. However, in 4,5% of people, initially normal level of immunity are transformed into moderate immunosuppression. All four variants of immune responses are virtually unmistakably predicted by a set of 20 predictors, which allows us to make adjustments to balneotherapy in advance. **Conclusion.** Immune responses to adaptogens are individual and conditioned by a number of predictors.

Key words: Immunity, Chronic Inflammation, Adaptogenic Balneotherapy, Immune Responses.