Predictors of individual immune responses to adaptogens

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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 Naftussya 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 phagocyte – Microbial Count MC or Right’s Index) and completeness.
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(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]:

\[ \text{BCCN} \ (10^9 \text{Bact/L}) = N \ (10^9/L) \cdot \Phi I \ (%) \cdot MC \ (\text{Bact/Phag}) \cdot \text{KI} \ (%) \cdot 10^{-4} \]

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

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

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]:

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

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

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:

\[ Z = (V/N – 1)/Cv \]

where

- \( N \) is Mean of Normal Variable,
- \( Cv \) 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 metod. 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.

| 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.

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.

| Variables currently in the model | Wilks’ Λ | Partial Λ | F-removal (3.2) | p-level | Tolerance |
|---------------------------------|----------|-----------|-----------------|---------|-----------|
| IgA Serum, g/L                  | .0016    | .711      | 2.85            | .062    | .396      |
| Bactericidity vs Staph.aur, 10⁹ Bacteria/L | .0016 | .720      | 2.73            | .070    | .125      |
| Popovych’s Leukocytary Strain Index-1, pts | .0044 | .264      | 19.5            | 10⁻⁵    | .029      |
| Lysozime Saliva, mg/L           | .0058    | .198      | 28.3            | 10⁻⁶    | .079      |

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

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
### Table 3.

Summary of Stepwise Analysis for Variables predicting various Immune responses.

The variables are ranked by criterion Lambda

| Variables currently in the model | Wilks’ Λ | Partial Λ | F-removal (3,2) | p-level | Tolerance |
|---------------------------------|----------|-----------|-----------------|---------|-----------|
| 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, 10⁶ CFU/g | .0015 | .748 | 2.36 | .101 | .165 |
| Microbial Count vs E. coli, Bacter/Phagocyte | .0035 | .330 | 14.2 | 10⁻⁴ | .047 |
| Bactericidty vs E. coli, 10⁹ 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 |
| Lysozyme Saliva, mg/L | .0017 | .689 | 3.15 | .046 | .339 |
| CD³⁺CD⁸⁺ 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 |

Next, the 20-dimensional space of discriminant variables transforms into 3-dimensional space of canonical roots, which are a linear combination of dis-
The canonical correlation coefficient is for Root 1 0.983 (Wilks’ $\Lambda=0.0012; \chi^2(210)=p<10^{-6}$), for Root 2 0.943 (Wilks’ $\Lambda=0.0337; \chi^2(127)=p<10^{-6}$) and for Root 3 0.834 (Wilks’ $\Lambda=0.3039; \chi^2(63)=p=0.005$). 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, 10⁶ 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   |
| Std Neutrophiles of Blood, % | -.841  | .165   | -.310  | -.819  | .160   | -.302  |
| IgG Serum, g/L   | .823    | -.530  | -.991  | .257   | -.166  | -.309  |
| E. coli faeces, 10⁶ CFU/g | -0.23   | -.354  | 1.426  | -.0002 | -.0030 | -.0121 |
| Microbial Count vs E. coli, Bacter/Phagocyte | -3.515  | .783   | -.1635 | -.494  | .110   | -.230  |
| Bactericidity vs E. coli, 10⁶ 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  | -.148  | -.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  |
| Erhityrocyturia, 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 | Eigenvalues | Cum. Prop. |
|------------------|-----------|-------------|------------|
|                  | -.37,96   | 28,119      | .732       |
|                  | 23,06     | 8,028       | .940       |
|                  | -.75,10   | 2,291       | 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](image1)

![Fig. 3. Individual values of the first and third roots in which condensed the information about predictors of various immune responses](image2)

**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 -0.129, R2 -0.006, R3 0.106 | -22.8   | -0.36    | +0.85    | +2.07    |           |
| Popovych’s Leukocytary Strain Index-1, pts | -0.109, -0.235, 0.041 | 0.215   | 0.141    | 0.203    | 0.127    | 0.067     |
| Bactericidity vs E. coli, 10<sup>9</sup> Bacteria/L | -0.078, -0.222, 0.095 | 1.154   | 0.71     | 0.80     | 0.99     | 0.99      |
| Bactericidity vs Staph. aur, 10<sup>9</sup> Bacteria/L | -0.078, -0.222, 0.095 | 1.30    | 0.75     | 0.85     | 0.98     | 106       |
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.

| Clusters                        | N/N | N/S (10) | N-S (10) | N-N (10) | Norm (30) |
|--------------------------------|-----|----------|----------|----------|-----------|
| N/N                            | 0   | 53       | 679      | 32       |           |
| S/S                            | 8.1 | 10^-2    | 0        | 592      | 21        |
| N/S                            | 16.8| 10^-6    | 14.0     | 10^-6    | 0         | 634       |
| N-N/N                          | 6.2 | 10^-4    | 2.9      | 15.4     | 10^-6     | 0         |

In Table 6, we present the squared Mahalanobis distances between clusters along with their F-values (df=20,2) and p-levels.
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.

| Clusters               | N/N | S/S | N/S | N-N |
|------------------------|-----|-----|-----|-----|
| **Variables**          |     |     |     |     |
| IgA Serum, g/L         | p=.409 | p=.227 | p=.045 | p=.318 |
| Bactericidity vs Staph. aur, 10⁹ Bacteria/L | -22,98 | -32,60 | -64,91 | -23,85 |
| Popovych's Leukocytary Strain Index-1, pts | -6,20 | -5,85 | -4,31 | -6,15 |
| 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 |
| Erthrocyturia, Ig/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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Predictors of individual immune responses to adaptogens

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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 Naftussya 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.