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Research Article

A STEPWISE SCREENING PROTOCOL TO SECURE THE MODULE-BASED TREATMENT FOR MANAGING IMMUNOPATHOLOGY

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ABSTRACT

The article presents the various options and levels for multistage screening and modular-type immunoprophylax is and immunotherapy, including for immunocompromised patients.

INTRODUCTION

In recent years, there has been asteady trend towardsthe decline ofherd immunity, resulting in an increase of up to 40-60% frequency of immune and immunodependent diseases (Kalinina *et al*., 2008; Novikov, 2009; Haitov, 2012). This requires the creation of a stepwise approach to detect and treat immunocompromised people. Immune imbalance has a pathogenic role in immunodependent disorders. Treatment is usually immunotropic. This group is composed of primary B- and T-dependent immunodeficiencies; immunodeficiencies combined with a high mortality rate; immunodeficiencies with failure in nonspecific factors - phagocytosis, and the complement system.

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It also includes HIV infection leading to AIDS, opportunistic infections, etc; onco- and lymphoproliferative diseases caused by suppression or excessive proliferation of the immune cells; allergic, autoimmune, immuno complex diseases. Immunoassociated disorders include diseases in which the immune imbalance hasan important, but not apathogenetic role. This group consists of secondary immunodeficiencies, infections, bronchopulmonary diseases, peptic ulcer, etc. Immunotropic treatment is subsidiary (Zemskov *et al*., 2015; Novgorod, 2012; Handbook of Clinical immunology, 2015; Haitov, 2011).

MATERIALS AND METHODS

Patient questionnaire: It's a computer program № 2014619643 for identifying immunodeficiency, infectious,

allergic, autoimmune, lymphoproliferative syndromes, chronic diseases (Certificate of state registration of the computer program, 2014). Immunodeficiency syndrome is diagnosed in the presence of 3 positive responses to the questionnaire; infectious syndrome and associated diseases - 2; autoimmune, lymphoproliferative (neoplastic), allergic syndromes - 1. Patients are considered "at risk" if they have one syndrome (excluding autoimmune or lymphoproliferative) and "at increased risk" if they have more than one syndrome. 2. Mathematical justification for candidates of minimal representative number for clinical and laboratory examination and integral analysis of grouped hematological, biochemical, bacteriological, immune changes and other clinical indicators, all in ranks.The rank is minimal (Rank 3) if significant changes of index occur in <33% of patients, medium (2) - in 33-66%, large (1) – in more than 66% (Zemskov *et al*., 2015).

Table 1 represents the data of the complex clinical and laboratory examination of patients with 3 chronic inflammatory diseases (Deep Bacterial Pyoderma, Chronic Pyelonephritis, Chronic Salpingo-oophoritis (Zemskov *et al*., 2015).

Designations:general - B, C, I, H – grouped bacteriological, clinical, immune, hematological indicators; Ce, Bd, P, Cy – cellular, B-dependent, phagocytic, cytokine levels of immunity; $^{H}_{1,2.3}$–differences in the ranks compared to the standard level; (+,-) vector of dynamics from the base level for all the indicators,HDF – Hematological Disorders' Formula; ISDF – Immune System Disorders' Formula; I, II, III – large, medium, minimal levels of differences; less the sum of ranks the greater the difference.MMMM – middle molecular mass molecules.

From Table 1, it appearsthat during the acute stage of inflammatory diseases, changes in general body-wide conditions were observed. Thus, in patients with Deep Bacterial Pyoderma large levels of change were calculated in bacteriological and clinical settings, and medium levels in immune and hematological parameters; in patients with Chronic Pyelonephritis medium levels were observed in bacteriological, clinical, hematological and immune settings; in patients with Chronic Salpingo-oophoritis medium levels were observed in clinical, immune, bacteriological settings and minimal levels in hematological parameters. Integral rating analysis shows max changes in clinical and laboratory parameters in Chronic Pyelonephritis, Deep Bacterial Pyoderma and Chronic Salpingo-oophoritis.

Laboratory evaluation of significant changes immunological parameters compared to the standard levels with determination of stimulation/suppression Sum vector

Results (Table 1) show that Deep Bacterial Pyoderma has almost similar indicators' variations - 25% / 29%, in Chronic Pyelonephritis and especially in Chronic Salpingo-oophoritist here has been shown prevalence in activation of the immune system - 50% versus 25% and 13%. 4. The application of frequency analysis of specific parameters and levels in a population of patients, which determines the risk of developing pathology, showed in Deep Bacterial Pyoderma the suppression of T-dependent parameters, the accumulation of immunoglobulins of three classes, circulating immune complexes, middle molecular mass molecules (MMMM); in Chronic Pyelonephritis it revealed the imbalance in T-cells subpopulations, inhibition of neutrophils' metabolism, stimulation of the formation of proinflammatory cytokines; in Chronic Salpingo-oophoritis – the imbalance in regulators subpopulations of T and NK-dependent parameters-ditch, activation of humoral reactions, production of cytokines, the number of CD95 + cells.

Evaluation of laboratory pathology by using variations of parameters in different levels of immunity

Table 1 shows that patients with Deep Bacterial Pyoderma predominantly had changes (> 66% of indicators) in humoral, phagocyte-mediated and cell-mediated immunity and insignificant changes (<33%) in cytokine-mediated immunity. The reactions of the immune system in Chronic Pyelonephritis and Chronic Salpingo-oophoritis were the same: significant changes observed in humoral and cytokine-mediated immunity, medium (33-66%) – in cell-mediated and phagocyte-mediated immunity. In other words, this method of analysis has not been representative.

Calculation of key parameters of immune disorders: The degree of comparability is calculated by using the Hematological Disorders' Formula (HDF) and Immune System Disorders' Formula (ISDF):

$$\left(\frac{\text{Patient ratio}}{\text{Normal ratio}} \cdot -1\right) \times 100\%$$

There is low (I) level of immune imbalance if changes in the values of parameters are <33%. Medium (II) level lies in interval from 33 to 66%. Patient has Severe level (III) of immune imbalance when changes in the values > 66%. In addition, indicators significantly different from the specified levels are selected from the total number of parameters studied by traditional statistical methods and the coefficient of diagnostic value (Kj) is determined using the formula:

$$Kj = \frac{2 \cdot (\delta_1^2 + \delta_2^2)}{(M_2 - M_1)^2}$$

where δ_1 and δ_2–root-mean-square deviation, M_1 - the arithmetic mean ofparameters in healthy persons, M_2 - - the arithmetic mean of parameters in patients from the Main group. The next step is to identify key indicators using the following interpretation: the smaller the absolute value Kj the higher the level of difference from specified level. It was evaluated (Table 1) that patients with Deep Bacterial Pyoderma ($L^+_3Neu^+_3Lymp^-_2$) have leukocytosis, neutrophilia and lymphopenia. In patients with Chronic Pyelonephritis ($Lymp^-_2Neu^+_2L^+_2$) medium lymphopenia, neutrophilia and leukocytosis were presented. And in patients with Chronic Salpingo-oophoritis ($Neu^+_2M^+_2L^+2$) there were neutrophilia, monocytosis and leukopenia. Information capacity of immune tests was higher. So in the case of Deep Bacterial Pyoderma ($CIC^+_3NKcells^+_3IL6^+_3$) indicators include stimulation of the circulating immune complexes' level, cytotoxic NK cells, interleukin 6; nephritis, in Chronic Pyelonephritis (B^+_3 $MMMM^+_3$ Tk^+_3) – B-cells, middle molecular mass molecules and cytotoxic T-cells; in Chronic Salpingo-oophoritis ($TNF^+_3IgG^+_3T^-_2$) - tumor necrosis factor, IgG, decreasing the number of T-lymphocytes.

Table 1. Changes in clinical and laboratory parameters in the acute stage of inflammatory diseases compared to the standard level

Disorder	General	Dynamic vector, %	Immunity level	Key indicators (HDP/ISDF)	Sum of ranks
Deep Bacterial Pyoderma	$B^{n}_{1}C^{n}_{1}I^{n}_{2}H^{n}_{2}$	+25/-29	$Bd^{n}_{1}P^{n}_{1}Ce^{n}_{1}Cy^{n}_{3}$	$L^{+}_{3}Neu^{+}_{3}Lymp^{-}_{2}$ / $CIC^{+}_{3}NKcells^{+}_{3}IL6^{+}_{3}$	12/II
Chronic Pyelonephritis	$B^{n}_{1}C^{n}_{1}H^{n}_{1}I^{n}_{2}$	+50/-25	$Bd^{n}_{1}Cy^{n}_{1}Ce^{n}_{2}P^{n}_{2}$	$Lymp^{-}_{2}Neu^{+}_{2}L^{+}_{2}/B^{+}_{3}MMMM^{+}_{3}Tk^{+}_{3}$	11/I
Chronic Salpingo-oophoritis	$C^{n}_{1}I^{n}_{2}B^{n}_{2}H^{n}_{3}$	+50/-13	$Bd^{n}_{1}Cy^{n}_{1}Ce^{n}_{2}P^{n}_{2}$	$Neu^{+}_{2}M^{+}_{2}L^{+}_{2}/TNF^{+}_{3}IgG^{+}_{3}T^{-}_{2}$	14/III

RESULTS AND DISCUSSION

I.MODULAR IMMUNIZATION AND IMMUNOTHERAPY

This implies drug prescription, which is an immunoactive drugs for the prevention and / or treatment of diseases.

Prevention module (PM): Is a method of individual or mass protection of the population from infectious diseases by creating or enhancing the specific artificial immunity. Views: 1 specific active – the injection of the vaccine / anatoxin; 2 - specific passive - serum proteins / antibodies; 3 – phage-vaccine – a combination of bacteriophages and antigens; 4 - active-passive - a combination of vaccines and serum specific proteins; 5 - nonspecific – an activation of the immune system during antigen-nonspecific infections (ARI) – i.e an injection of immunoglobulins from healthy donors; 6 - a variety of traditional drugs regarding changes in the immune system of a patient with immunotropic-oriented action of the drugs.

Monovalent medical module (MLM): Is the use of pharmacological or non-pharmacological immune monotherapy for the prevention or correction of changes in immune system function. Indications: being in a risk group (depletion, obesity, severe menopause, elderly age, etc); unsuccessful traditional treatment of the disease during the month; immunodeficiency of 2-3 degrees with 1-2 parameters or 1 degree – with 3-5 parameters simultaneously; protracted disease; allergic or autoimmune complications; atypical temperature - low-grade fever more than 10-12 days, the strong/ weak fever or the absence of fever completely during acute ininfection.

Types of immunotherapy: 1 - specific active stimulating - therapeutic vaccines; 2 - specific adaptive - transfer factor; 3 - specific passive substitutional - antibodies; 4-specific passive overwhelming - antibodies; 5 - nonspecific activity stimulation - adjuvants, modulators; 6 - nonspecific adaptive boosting (Timo / myelopeptides); 7 - non-specific passive substitutive - antibodies, immune cells; 8 - nonspecific suppressive - steroids, cytostatics; 9 -systemic - the impact on the basic components of the immune system (T-, B-, phagocytic); 10 - local –activation of local resistance in organs interacting with the external environment; 11 - metabolic, secondary – metabolits, vitamins, membrane-protectors, energizers, adaptogens; 12 - non-pharmacological - ozonated solutions, sorption methods, plasmapheresis, physiotherapeutical methods - laser, ultrasonic, ultraviolet and magnetic infrared laser irradiation, and others.

Polyvalent medical module (PMM): Is polyvalent immunotherapy, i.e. simultaneous or consequent assignment of several drugs or procedures with different mechanism of action to address immune disorders and improve the efficiency of traditional treatment of diseases.

Indications: chronic (more than 3 months), recurrent course of the main pathological process; pronounced intoxication syndrome with metabolic disorders, secondary complications (worm infestation), etc.; unsuccessful immune monotherapy during the month; the complex nature of immunopathology - high (three) deficient, the combined defeat in T-B-units, populations, subpopulations lymphocytes, phagocytes, multidirectional dynamics parameters.

Types of immunotherapy: 1 - immuno-metabolic - a combination of modulators with metabolics / antioxidants; 2 - pharmacological and non-pharmacological - sequential or simultaneous usage of pharmacological and non-pharmacological correctors; 3 - local-systemic - a combination of modulators of local and systemic immunity; 4 - combined - two pharmacological correctors or non-drug factors to the different mechanisms of action; 5 -adjuvant active - vaccine and adjuvant / modulator; 6 - adjuvant passive – serum and adjuvant / modulator; 7 - alternative - simultaneous or sequential usage of stimulants and suppressors of defense reactions; 8 - complex - a combination of more than two immunotropic substances; 9 - consistent complex – usage of 2-3 correctors with different mechanism of action during course of metabolic cocktails with an interval of 2-3 weeks.

STEPWISE IMMUNOTHERAPY PRESCRIPTION

The principal choice of mono- or polyvalent medical and preventive modules is implemented with regard to clinical data; selection of specific immunotropic drugs is based on the following data.

Purpose of the provisional adaptogenic immunotherapy based on syndromes of immunopathology excluding nature of diseases

According to the data, persons belonging to the risk group receive adaptogens – Chinese lemongrass, eleutherococcus, ginseng and small immunocorrectors - apilak, dibazolum, yeast, vitamins, pre-, pro-, synbiotics; patients at high risk also have prescriptions to combination of 2-3 adaptogens or modulators of a broad-spectrum (sodium nucleinate, thymomimetics, myelopeptides) (computer program № 2014619643) (Certificate of state registration of the computer program, 2014).

Supporting immunotherapy with traditional treatment (certificate on computer program №2015612811) **(**Certificate of state registration of computer program, 2015**).** Correction for laboratory disorders in patients in dependence on the type of immune disorders can be carried out with targeted selection of traditional drugs that stimulate the immune system (metabolics *et al*.) and restriction of drugs that suppress it (corticosteroids, etc.). In autoimmune and allergic diseases, we've applied reverse tactics. With the development of pseudoallergies it was recommended to use antispasmodic, choleretic drugs, enteral

sorbents. With problems of the digestion, absorption of peroxide-oxidation of lipids, antioxidant protection, disnucleotidozes and others it is recommended metabolic treatment to use, including enzyme medicine (festal, panzinorm, pancreatin); native nucleic acid derivatives (sodium nucleinate, derinate, ridostine), their synthetic analogues (izoprinozin, synthetic polynucleotides, poludane); biologically active compounds with membrane-protective properties: energizer - riboflavin, nicotinamide; free fatty-acids – pantothenate; activator of glycolysis – thiamine, inosine; stimulants of β-oxidation - biotin, thiamine, lipoate; antioxidants - beta-carotene, retinol, alpha tocopherol, ascorbic acid, ubiquinone; polinenasy-whelping phospholipids, hepatic - essentiale, Karsil, lipostabil, phosphoglyph.

Simplified usage of immunotherapy based on key immune pathology in specific diseases (certificate to the computer program № 2015614977) (Certificate of state registration of computer program, 2015). At this level, patients' immune status analysis is not performed; the leading factor has become the disease. Options of immunotherapy will be selected on the basis of matches within the known modulators and target key parameters previously defined by the Immune System Disorders' Formula (ISDF) at individual nosology. For example, according to the key ISDF ($CIC^{+}_{3}NKts^{+}_{3}IL6^{+}_{3}$) for patients with acute purulent pyelonephritis modulators should be prescribed, they have an ability to reduce level of aggressive circulating immune complexes, cytotoxic natural killer cells and pro-inflammatory interleukins.

Selection of immunotherapy based on generalized characteristics modified parts of immunity, without taking into account the type of diseases (computer program № 2015612811) (Certificate of state registration of computer program, 2015). The drugs are selected by the coincidence of critical indicators of altered patient group feasted on the links-target correctors. For example, if a patient is determined by deficit of the cell-level, he/she is recommended to use Anabole, Amixine, Bronhoimmunale; for B-cells deficiency - Gepone, Dalargine, Mielopide; for phagocytic deficiency - Diutsifone, Izoprinozine, Derinate.

Personalized selection of immunotherapy based on formulas of targets for immunocorrections in specific diseases. The essence of the computer programs № 2014660956 and № 2015619428 is the combination of laboratory parameters of the patient with the previously defined key parameters tested variants of immunotherapy (Certificate of state registration of computer program, 2014). For example, formula for targets of immune correction - Superlymph for patients with exacerbation of chronic pyelonephritis includes - $NKr^{-}_{3}NKt^{-}_{3}IL4^{+}_{3}$, therefore, if a patient with the disease is determined with the accumulation of the 3rd degree of regulatory and cytotoxic natural killer, the recommended drug is Superlymph.

Conclusion

Through the use of additional methods of clinical and laboratory studies evaluating the outcome of patients with various diseases developed multi-step - from simple to complex, from the systemic to the local, the algorithm of detection and treatment for immunocompromised patients using preventive, mono and polyvalent therapeutic modules.

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