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Experience of bacterial lysates application in treatment of respiratory diseases

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Respiratory diseases traditionally remain the most common diseases; they are registered at 30 % of adult and 50 % of minor population. This trend determines necessity of further development of methods for their efficient treatment and prophylaxis. That's why during the last years application of immunotropic (especially modern immunomodulating) preparations for treatment of respiratory diseases is believed to be promising direction of practical medicine. This type of immune therapy contributes to significant decrease of risk of their development, decreases frequency of relapses and development of chronic pathologic process, ensures relief of clinical symptoms of respiratory diseases of infectious nature, makes it possible to prevent development of complications, and to correct secondary immunodeficiency. This type of immune therapy also ensures significant improvement of treatment of this category of patients, amelioration of their quality of life, decrease of treatment and prophylaxis costs for the patient and community.

In 2006 the experts of National Academy of Science of the USA and Committee [13] for new directions in research of antibacterial therapy stated and proved principally new concept of strategic approaches and scientific development of innate immunity activators – the innovative medical preparations for treatment of infectious diseases. This concept is based on the following principles:

- 1) Treatment of infectious diseases by immune system modulation;
- 2) Dominant part of antibacterial agents which caused revolution in treatment of infectious diseases during the last years, are received from bacterial products;
- 3) Immunomodulators may be efficient in combination with traditional antibacterial and anti-viral preparations;
- 4) Innate immunity, like antibacterial therapy, acts quickly and after onset of its effect acts on the various microorganisms.

That's why potential advantages of immunomodulating therapy include the following:

- 1) Immunomodulators do not act directly on the microorganisms, so they may void the problem of antibacterial resistance development;
- 2) Immunomodulators may offer new options for treatment of patients with disturbed immunity, when traditional preparations are not sufficiently efficient;
- 3) Immunomodulators have potentially wide spectrum of action against bacterial, viral and mycotic infections.

On the background of respiratory diseases the syndrome of secondary immunodeficiency may develop; it is a complex of features evidencing immune system disorders formed in late postnatal period or in adults. Its clinical manifestations include chronic diseases with long course, often with relapses, resistance to the traditional therapy, development of complications, etc. Clinical (collection of immunologic anamnesis, physical examination) and laboratory immunologic analytical methods are used to diagnose secondary immunodeficiency.

The list of most common diseases associated with secondary immunodeficiency and requiring immunologic examination, according to R. M. Khaitova and N. I. Ilyina [1], includes:

- 1) Generalized infections: sepsis, purulent meningitis, etc.;
- 2) Chronic bronchitis with frequent relapses and pneumonias in anamnesis combined with otolaryngological diseases (purulent sinusitis, otitis, lymphadenitis), torpid to the normal therapy;
- 3) Pneumonias with frequent relapses;
- 4) Multiple bronchoectasis;
- 5) Chronic bacterial infections of skin and subcutaneous cellular tissue (pyoderma, furunculosis, abscesses, phlegmons, septic granulomas, relapsing periproctitis in adults);
- 6) Chronic mycotic lesions of skin and mucous tunic, candidosis, parasitic diseases;

- 7) Relapsing aphthous stomatitis combined with increased frequency of acute respiratory inflammatory infections;
- 8) Relapsing herpes viral infection of various location;
- 9) Gastroenteropathy with chronic diarrhoea of unclear aetiology, intestinal dysbacteriosis;
- 10) Lymphadenopathy, relapsing lymphadenitis;
- 11) Long-term subfebrility, fever of unclear genesis.

The following types of secondary immunodeficiency are described:

- a) Compensated, which is manifested as increased vulnerability for infectious agents in form of often acute respiratory inflammatory infections, pneumonias, pyodermas, etc.;
- b) Subcompensated, which is featured by disposition to transfer of infectious processes in chronic forms with development of often pneumonias, chronic bronchitis, duodenitis, pancreatitis, cholecystitis, pyelonephritis, etc.;
- c) Decompensated, which is manifested as generalized infections; their aetiology is determined by opportunistic pathogenic bacteria of malignant neoplasms. For example, AIDS is a decompensated form of secondary immunodeficiency.

The following forms of secondary immunodeficiency are distinguished in clinical practice:

- 1) Infectious;
- 2) Allergic;
- 3) Autoimmune;
- 4) Immune proliferative (lymphatic proliferative);
- 5) Combined.

Non-allergic chronic and relapsing respiratory diseases are featured by infectious syndrome of secondary immunodeficiency. It may be connected with T-cell or humoral (B-cell) immunity disorder, their combination and defects of non-specific factors of body resistance. That's why modern principles of treatment and prophylaxis of respiratory diseases provide for complex approach to resolution of this problem, including basic immunotropic therapy. This therapy is a complex of etiotropic and pathogenetic measures having potential to influence on various elements of immune system and, as a result, capable to alter activity, character and direction of immune responses.

Immunotropic therapy is an important method of treatment of patients suffering from respiratory diseases with secondary immunodeficiency. There are 3 principal directions of immunotropic therapy [1]:

- 1) Active immunization (vaccination);
- 2) Substitution therapy (blood preparations: plasma, immunoglobulins, leucocytic mass, etc.);
- 3) Immunotropic preparations (immunostimulators: G-M CSF; immunomodulators of exogen and endogen origin, chemically pure and synthesized).

Immunomodulation is one of the most promising measures for clinical application aimed at return of immune status to the original normal level in case of various pathologic conditions. Immune rehabilitation is actively developing during the last years. Immune rehabilitation is the rehabilitation of functional activity of human immune system and health with use of complex of medications and non-medication remedial measures [3].

Immune response is a complex process of interaction of various cells determined by synergy of various elements of

immunity, such as cytokine synthesis, cellular receptor expression, enzyme activation, development of cellular sensitization, antibody synthesis and normal homeostasis. That's why for administration of suitable immunotropic therapy the clear understanding of mechanism of immune system dysfunction in case of various pathologies is required, but, unfortunately, it is possible not in all cases. That's why practitioners have different attitude to this type of therapy, ranging from unconditional acceptance and up to complete absence of wish to use any immunotropic medical preparations.

Selection of the certain type of immune therapy is determined by intensity of acute infectious inflammatory process and defects in immune system function revealed in patients suffering from respiratory diseases. Thus, therapy in form of vaccination is used for prophylaxis during remission of infectious and somatic diseases. Substitution therapy may be used at any stage of infectious inflammatory process, including the acute condition. Immunomodulators may be used at any stage of infectious inflammatory process, but more often they are used in case of remission. General principles of immunomodulator administration include [1]:

- 1) Administration in complex with etiotropic therapy, immunomodulator monotherapy is acceptable only at the stage of remission of infectious process;
- 2) Selection of certain medical preparation and scheme of its administration are determined by intensity of acute infectious inflammatory process, its aetiology, character of immune defect taking into account somatic diseases and induced influences;
- 3) Main criteria of immunomodulator administration are clinical manifestations of syndrome of secondary immunodeficiency – existence of infectious inflammatory process which is torpid for adequate etiotropic therapy;
- 4) Doses, schemes and duration of treatment are to conform to the instruction on use of medical preparation; their correction should be performed by experienced clinical immunologist only;
- 5) If medical institution benefits from appropriate resources and equipment, it is recommended to use immunomodulators together with immunologic monitoring;
- 6) Change of any parameter of immunity revealed during immunological examination at generally healthy subject is not a sufficient basis for immunomodulating therapy, such subjects are to be monitored by immunologist.

Reasonability of immunotropic preparations administration in case of acute bacterial and viral respiratory infections is a complex problem which is not completely resolved yet. Thus, administration of preparations with dominant stimulating properties (for example, thymus preparations) in case of acute processes may aggravate their course because of excessive cytokine production. When cytokines are used for immune therapy, it should be taken into account that they are indicated in leucocytopenia, lymphopenia and low spontaneous neutrophil activation, in other cases they may provoke severe systemic inflammatory response and septic shock. Preparations with dominant immunomodulating, not stimulating properties (for example, preparations of muramylpeptide class) are more appropriate in such cases, as they are capable not only to stimulate suppressed elements of immune

system, but also to decrease excessive activity of immune competent cells. In case of acute inflammatory diseases with intoxication syndrome immunomodulators with detoxication and antioxidant properties should be preferred. Immunomodulator use in case of acute infectious processes is justified for the people of secondary immunodeficiency risk group with high probability of development of post-infectious complications or long-term course of the main disease.

During the last years the interest in respiratory diseases treatment with such immunomodulating preparations as lysates of bacteria which are prevailing agents of respiratory infections is growing due to the following factors. First, bacterial lysates are featured with double mechanism of action: specific (vaccine-like) and non-specific (immunomodulating). Second, specific active immunization against the most common agents causing respiratory diseases is advantageous to compare with non-specific immune stimulation due to its target effect and efficiency. Third, specific vaccines against main part of respiratory pathogens are absent or are not efficient due to the quick variability of respiratory pathogens and short period of efficient specific immunity to them. Fourth, bacterial lysates may be administered during the acute stage of the disease, including in combination with etiotropic therapy, and for prophylaxis, in order to form specific immunity to the certain agent causing respiratory infection.

Thus, bacterial lysates initiate specific immune response to the pathogens contained in them due to the contact of antigens of the most important agents causing respiratory infections with macrophages on the surface of mucous tunic of respiratory tract and alimentary canal with their further presentation by lymphocytes of MALT system (lymphoid tissue associated with mucous tunic). As a result, committed clones of B-lymphocytes appear to produce specific antibodies to antigens of infectious agents contained in immunotropic preparations of bacterial origin. Migration of such B-lymphocytes in the other lymphoid structures of MALT-system and their further differentiation in plasmocytes result in production of specific secretory immunoglobulin (IgA) and development of efficient local immune protection against main agents causing respiratory diseases. Bacterial immunomodulating preparations are destined to stimulate specific response of the body to pathogenic effect of those microorganisms, the antigenic substrates of which are included in preparations, that's why their intake induces specific response in the system of local immunity and system of general immunity as well – in such a way they have vaccination-like effect. So, bacterial lysates are destined to stimulate specific response of the body to pathogenic influence of those microorganisms, the substrates of which are contained in the preparation. In addition, they are capable to improve general body resistance causing positive preventive effect in case of respiratory infections [16, 23, 28].

Depending on the way of use bacterial lysates are classified as local and systemic preparations. Clinical experience accumulated during the last years evidences low efficiency of bacterial lysates having local effect; this may be explained by the following factors:

- Short period of contact of preparations with mucous tunic;

- Capture, due to the reasons mentioned above, by respiratory mucous tunic of small part of antigenic substances;

- Constant washing with saliva of oropharyngeal area where cilia epithelium does not function is an obstacle for constant contact of preparation with immune competent cells;

- Absence of data about time of effect of bacterial lysates in case of their local application.

It should be underlined that similar results were received earlier for local antibacterial therapy – now it is used only for treatment of otitis [8]. In addition, existing situation evidences unjustified wide use of antibacterial agents in patients who often suffer with these diseases – this practice causes dysbiotic responses of oropharyngeal segment, in some cases – complete absence of obligatory microflora. All these factors make it possible to suppose that bacterial lysates are capable to compensate lack of immune system stimulation caused by bacterial infection, and to cause long-lasting positive adaptogenic influence on this system. Taking into account all mentioned above, bacterial lysates having systemic action are the most wide-spread in treatment of respiratory diseases. One of them is Broncho-Vaxom; the lysate of 8 bacterial pathogens which are the most often causes of respiratory infections.

Mechanism of immunomodulating effect of Broncho-Vaxom is well established in experimental and clinical conditions. It has positive effect on various elements of immune response [10, 15, 16, 23, 25, 26, 31, 37], particularly:

- it stimulates functional and metabolic activity of macrophages, including alveolar macrophages, against infectious agents and neoplasm cells;
- it stimulates B-cell activity, increasing production of specific antibodies to the pathogenic microorganisms;
- it increases the number and activity of T-helpers;
- it increases level of secretory IgA in saliva, respiratory mucous tunic, bronchoalveolar lavage fluid, stomach secretion;

- it increases dendrite cell activity;
- it increases IgG, IgM and IgA levels in serum;
- it stimulates activity of NK-cells (“natural killers”);
- it stimulates production of a number of important cytokines, including: INF- (-interferon), IL-1, 2, 6, 8, TNF- (tumour necrosis factor), neutrophil-activating factor, prostaglandin E2, -interferon;

- it improves interaction of immune competent cells among them, normalizes immunoregulating index;
- it decreases suppressive activity of T-lymphocytes;
- it decreases IgE level in serum.

All this ensures that Broncho-Vaxom:

- not only stimulates, but modulates immunity;
- has vaccination-like effect;
- has systemic immunomodulating effect;
- not only causes antigen-specific immune response, but influences on all non-specific factors of immune system.

Broncho-Vaxom advantages include the fact that it is used not only for treatment, but also for prophylaxis: 1 capsule once a day in case of all respiratory diseases of infectious origin. During the acute period of the disease the course lasts for 10–30 days. Prophylactic course is 10 days each month during 3 subsequent months. For administration to children

the same preparation containing half-dose (3,5 mg) of bacterial lysate is used, for adults normal dose (7 mg) is administered.

As it was already mentioned above, Broncho-Vaxom is a preparation studied well in clinical practice. Its efficiency and safety was demonstrated in 43 randomized double-blind placebo-controlled studies in children and adults. More than 6000 patient participated in these studies; since 1990 this preparation was administered to more than 60 mln of patients of various age. Data evidencing high efficiency and safety of bacterial lysates are presented in more than 100 scientific publications. Dominant part of studies of efficiency and safety of preparation was performed among the children suffering from often respiratory infections, and among the adults with chronic obstructive lung diseases and chronic bronchitis. Thus, administration of Broncho-Vaxom to 220 children with recurrent respiratory infections resulted in proven decrease (for 24 % during 6 months) of frequency of the relevant infections [33]. In the other study [9] administration of this preparation resulted in significant (for 10 % and more) decrease of frequency of relapses in 232 children with recurrent diseases of upper respiratory tract.

Similar results were demonstrated in the third study [18], administration of course of Broncho-Vaxom to children resulted in decrease for 37 % of frequency of exacerbation of respiratory infections, decreased their severity for 42 % and decreased for 45 % administration of antibacterial preparations, leading, accordingly, to the decrease of potential side effect of antibacterial agents and prophylaxis of development of chemical resistance of respiratory pathogens. Similar data were received in study [19], its results demonstrated that administration of Broncho-Vaxom in recurrent respiratory infections in children decreased for 52 % general frequency of infectious pathology, decreased for 50,6 % frequency of infections of upper respiratory tract, for 68 % – frequency of otites and for 73,7 % – duration of episodes of exacerbation of respiratory infections.

Author of the work [32] performed meta-analysis of final data of 8 randomized blind placebo-controlled studies including in total 851 children with recurrent respiratory infections. It was established that Broncho-Vaxom course lasting for 6 months decreased in average for 35 % the frequency of exacerbations of respiratory infections in children. Similar results (decrease for 31 % of frequency of exacerbation of respiratory infections) were received in the other randomized blind placebo-controlled study [30], during 12-months follow-up of 75 children with recurrent bronchobstructive syndrome.

The works described below demonstrate efficiency of bacterial lysates in patients with hypogammaglobulinemia and general variable immunologic deficiency suffering from relapsing respiratory infections. Increased level of IgG, IgA [29] in serum was observed in patients suffering from relapsing respiratory infections after treatment with Broncho-Vaxom. In addition, in patients with general variable immunologic deficiency after intake of bacterial lysates IgA level increased [22]. Administration of immunoglobulins together with bacterial lysates increased efficiency for this categories of patients.

So, Broncho-Vaxom should be recognized as high-efficient and safe immunomodulator of systemic action in children

with often and recurrent respiratory diseases; in case of treatment in courses it decreases the number of cases of acute infectious respiratory diseases and their relapses, significantly decreases duration and severity of acute episodes of the disease, decreases necessity to administer antibacterial and other medical products, improves or completely stabilizes childish immune system function.

High efficiency of Broncho-Vaxom was demonstrated in a series of studies in adults. In several randomized placebo-controlled studies therapeutic efficiency of Broncho-Vaxom was demonstrated for 40,0–74,5 % of patients suffering from chronic bronchitis and chronic obstructive lung disease [14, 15]. In other similar study of 354 elderly patients it was demonstrated that Broncho-Vaxom decreased for 40 % frequency of infectious exacerbations in adult patients with chronic obstructive lung disease, and decreased for 28 % total number of infections of lower respiratory tract [27]. Broncho-Vaxom administration for prophylaxis of exacerbations of chronic obstructive lung diseases in double blind study [11] of 381 patients resulted in decrease for 30 % of frequency of patient hospitalization, and for 55 % of duration of hospitalization giving significant decrease of treatment costs.

Positive results of bacterial lysate administration to adult patients with chronic bronchitis were confirmed by data of the other studies. As a result of prophylactic administration of Broncho-Vaxom to patients with chronic obstructive lung disease frequency of exacerbations decreased significantly (for 24 % during 6 months), their severity also decreased (for 41%), the need to prescribe antibacterial agents decreased (for 24,5–37,0 %), the need to prescribe 2-agonists decreased (for 20 %), the need to prescribe mycolitics also decreased (for 50 %) [21, 24, 35, 36]. It was also noted [17] that clinical efficiency of preparation closely correlated with its positive immunologic effects. In double blind placebo-controlled study [15] of 256 elderly and aged patients decrease of frequency and severity of chronic bronchitis exacerbations was demonstrated together with decrease of frequency of administration of antibacterial agents to the patients receiving Broncho-Vaxom. Similar results were received in the other double blind placebo-controlled study [36], during 6-months follow-up of 428 patients with chronic obstructive lung disease. In addition, the authors of works [20, 31] believe that Broncho-Vaxom in patients with chronic bronchitis and chronic obstructive lung disease stimulated increased production of secretory IgA not only due to the fractions specific to the pathogenic microorganisms contained in this preparation, but also due to the increased production of a number of cytokines (interleukine-6 and -8) causing activation of non-specific protective mechanisms (system of interferons, etc.). There are reports [34] about reliable efficiency of Broncho-Vaxom use for prophylaxis of lung exacerbations in postoperative period in patients with respiratory diseases. Broncho-Vaxom is also efficient in otolaryngologic diseases in adults [4] as it contributed to the decrease of frequency, severity and duration of infections of upper respiratory tract, gave 2-fold decrease of frequency of their exacerbations, decreased patients' need in additional antibacterial therapy, improved their quality of life, and decreased costs for treatment.

So, the above-mentioned data evidence that Broncho-Vaxom in adults may be successfully used in chronic bronchitis and chronic obstructive lung disease in order to decrease frequency of exacerbations of these diseases, facilitate and shorten their course, decrease frequency of antibacterial agents, broncholitics and mycolitics prescription. Recognising high efficiency of this preparation in patients with chronic bronchitis and chronic obstructive lung disease, its good tolerance should also be noted. In multicenter double blind study [14] of 104 patients with chronic bronchitis receiving Broncho-Vaxom decrease of frequency and severity of exacerbations of the disease was registered. Side effects (nausea and abdominal pain) were observed at one patient only. Similar results were demonstrated in the other multicenter double blind study of patients with chronic obstructive lung disease [36]. In general, results of the above-mentioned global clinical studies demonstrated that frequency of non-serious and transient side effects in process of Broncho-Vaxom use in clinical practice does not exceed 3–4 %.

Pharmacoeconomic data also evidence promising perspectives of Broncho-Vaxom application in respiratory diseases. Meta-analysis [38] of the results of 4 double blind placebo-controlled studies demonstrated that Broncho-Vaxom administration to children with frequent respiratory diseases decreased quantity of days out of school, quantity of sick-lists prescribed to the parents for child care, decreased costs for purchase of medical preparations and total costs for the patient and community. In addition, the study [12] demonstrated that this preparation decreased costs for the patient and community for hospitalization of patients with severe exacerbations of respiratory diseases, as administration of preparation decreased for 30 % the risk of hospitalization to compare with placebo, decreased for 55 % duration of hospitalization, decreased for 44 % average costs for hospitalization and for 36 % – total value of hospitalization. Selection of optimum quality of immune therapy courses is an important issue in administration of bacterial lysates. It was an objective of a number of clinical studies. Oral administration of bacterial lysates to the volunteers for 10 days resulted in important increase of IgA level in saliva, a month after termination of intake of preparation this level returned to the primary value. The same volunteers after repeated prophylactic course of treatment had high IgA level during 3 months [29]. It should be noted that administration of only one course of bacterial lysates does not result in complete elimination of episodes of respiratory infections – it may be possible after several courses of therapy [2, 5–7].

Bacterial lysates are mainly used as the element of complex therapy, nevertheless, monotherapy with them is justified during immune rehabilitation measures. This approach is suitable for immune rehabilitation of patients not completely treated from acute infectious broncho-pneumonia process (residual manifestations of bronchitis, laryngitis, tracheitis), patients with cancer in order to improve their quality of life, it is often applied to the patients, suffering frequently and for a long time during the period of autumn and winter, especially in ecologically unfavourable regions which cover main part of the territory of Ukraine.

So, administration of bacterial lysates having systemic effect makes it possible to decrease frequency of development of acute respiratory diseases, exacerbations of recurrent and chronic respiratory diseases, to minimise the risk of quick progression of inflammatory process, to decrease frequency of exacerbations of chronic otolaryngologic diseases (rhinitis, sinusitis, laryngitis, tracheitis), to decrease frequency of relapsing infection in case of recurrent acute respiratory diseases. Administration of bacterial lysates having systemic effect contributes to stabilization of immune system function, decreases necessity to prescribe the other medical preparations, decreases total costs for patient treatment, making it absolutely justified from general clinical and pharmacoeconomic points of view. These facts should contribute to development of their wide recognition in clinical practice.

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ДОСВІД ЗАСТОСУВАННЯ БАКТЕРІАЛЬНИХ ЛІЗАТІВ ПРИ ЗАХВОРЮВАННЯХ ОРГАНІВ ДИХАННЯ

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Резюме. В статті представлена характеристика найбільш типових порушень функції імунної системи при захворюваннях органів дихання, що реалізуються у розвитку інфекційного синдрому вторинної імунної недостатності. Звернено увагу на особливості перебігу даного синдрому та можливі варіанти його корекції. Відмічено, що перспективними препаратами для лікування та профілактики рецидивів та хронізації захворювань органів дихання є бактеріальні лізати системної дії. Показано ефективність та безпечність використання при захворюваннях органів дихання у дітей та дорослих бактеріального лізату Бронхо-Ваксом. Показано перспективи його застосування у клінічній практиці з позицій фармакоекономіки.

Ключові слова: захворювання органів дихання, вторинна імунна недостатність, імуномодулятори, бактеріальні лізати, терапевтична та фармакоекономічна ефективність.

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EXPERIENCE OF APPLICATION BACTERIAL LYSATES WITH RESPIRATORY DISEASES

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Summary. The article describes the most typical dysfunction of the immune system in diseases of the respiratory system, implemented in the development of infectious syndrome secondary immune deficiency. Attention is paid to the peculiarities of this syndrome and its possible correction. It is noted that promising drugs for the treatment and prevention of recurrence and chronic respiratory diseases are bacterial lysates systemic effects. Showing efficacy and safety of respiratory diseases in children and adults bacterial lysate Broncho-Vaxom. Showing prospects of its application in clinical practice from the standpoint of pharmacoeconomics.

Key words: respiratory diseases, secondary immunodeficiency, immunomodulators, bacterial lysates, therapeutic and pharmacoeconomic efficiency.

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