

**EFFECTIVENESS OF IMMUNO-CORRECTING THERAPY IN CHILDREN IN THE  
COMPLEX TREATMENT OF CHRONIC BRONCHITIS**

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**ABSTRACT**

**Background:** The frequency of respiratory diseases remains one of the urgent problems of modern pediatrics, determining the high level of childhood morbidity, infant mortality, and disability in adolescence. **Objective:** We examined 55 children aged 4 to 7 years with chronic bronchitis. **Methods:** The concentration of cytokines IL-1 $\beta$ , IL-4, TNF- $\alpha$  in the blood serum was determined by enzyme-linked immunosorbent assay in the dynamics of treatment with the inclusion of immunocorrective drugs Bioflazid and Ribomunil. **Result:** It was found that the initial level of TNF $\alpha$  and IFN $\gamma$  in sick children was significantly higher, and the level of IFN $\gamma$  was significantly lower than the values of the control group. Sick children comprised 2 groups: group 1 — 25 children, in whose traditional treatment the drug Bioflazid was connected; Group 2 - 30 children, to the traditional treatment of which Bioflazid and Ribomunil were connected. **Conclusion:** It is shown that the inclusion in the complex therapy of drugs with immunocorrective effect contributes to the positive dynamics of clinical and immunological parameters.

**KEYWORDS:** chronic bronchitis, cytokines, immunocorrection, Bioflazid, Ribomunil.

**INTRODUCTION**

The frequency of respiratory diseases remains one of the urgent problems of modern pediatrics, determining the high level of childhood morbidity, infant mortality, and disability in adolescence.<sup>[1,3,4,5]</sup> Particular attention is paid to recurrent and chronic diseases of the bronchopulmonary system. Chronic inflammatory process in the bronchopulmonary system may be due to the presence of an immunodeficiency state. In the immune status of these children, a Th2-type response is often formed transiently with overproduction of IL-4 and IL-5, which stimulate high production of IgE by B-lymphocytes against a background of decreased synthesis of IgA, IL-2 and  $\gamma$ -interferon.<sup>[2,6]</sup>

The primary task in the rehabilitation of such children is the focus of therapy on reducing the intensity of antigenic exposure and increasing the resistance of the macroorganism in order to increase the effectiveness of immune defense factors.

The aim of this study was to study the dynamics of the content of serum cytokines (TNF $\alpha$ , IFN $\gamma$  and IL-4) in children with chronic bronchitis as a result of complex therapy with the inclusion of immunocorrective drugs.

**MATERIALS AND RESEARCH METHODS**

A clinical and laboratory examination of 55 children aged 4 to 7 years who were in the department of pulmonology of the Andijan regional multidisciplinary medical children's center was carried out. The criterion for inclusion in the group of patients was a frequent exacerbation of bronchitis (3 or more times) per year. The distribution of the groups: 1st group - 25 children, in the traditional treatment of which the drug Bioflazid was connected; Group 2 - 30 children, the complex treatment of which was connected Bioflazid and Ribomunil. Exclusion criteria - the presence of any autoimmune diseases that could have a significant impact on the function of the immune system. For children from group 1, the drug Bioflazide was prescribed against the background of basic therapy, 5 drops 1 time per day for 1 month, children of the 2nd group against the background of basic therapy + Bioflazid (5 drops 1 time per day for 1 month) and + Ribomunil according to the instructions for 3 months. Immunological examination was carried out before treatment, one month and 3 months after treatment. 18 healthy children of the same age made up the control group.

The concentration of IFN, IL-4, TNF- $\alpha$  cytokines in blood serum was determined by enzyme-linked

immunosorbent assay (LLC "Cytokine", S. St. Petersburg).

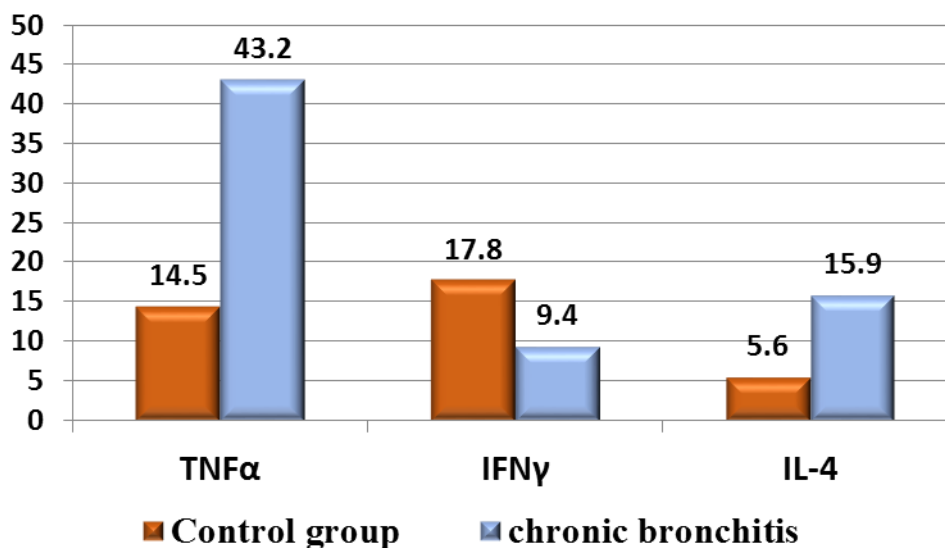
Statistical processing of the results was carried out using application software for statistical data processing Statistica® version 6.0. The significance of differences between the compared groups was evaluated by student criteria. Differences in the compared values were recognized as statistically significant at  $p < 0.05$ .

**The results of the study.** Analysis of the premorbid background of patients showed that 52.7% (29) of children had anemia of I-II degree. Atopic dermatitis is found in 29% (16) of children. From concomitant and transferred diseases, it was found that 89.1% of the examined had diseases of ENT organs. 14.5% of children experienced food allergies. Drug allergies were recorded in 5.4%. Bacterial-viral infection (83.6%) preceded an exacerbation of chronic bronchitis. Delayed physical development was observed in 25.4% of sick children.

Upon admission to the hospital, the main complaints of patients in 100% of cases were coughing. Lethargy was observed in 40% of the examined children, an increase in temperature was in 52.7%, an asthma attack was observed in 58.2% of the examined.

Humoral factors of immunity include mediators of a non-immunoglobulin nature that mediate the interaction between cells during the immune response - immunocytokines.

Analysis of the initial data of sick children showed that the level of TNF $\alpha$  was almost 3 times higher than the values of the control group ( $43.2 \pm 1.8$  pg / ml versus  $14.5 \pm 0.7$  pg / ml in the control,  $P < 0.001$ ), ( fig. 1). While the level of interferon- $\gamma$  was 1.9 times lower than the control values ( $9.4 \pm 0.8$  pg / ml versus  $17.8 \pm 1.0$  pg / ml in the control,  $P < 0.01$ ). The level of IL-4 in sick children was 3 times higher than the control values and averaged  $15.9 \pm 1.2$  pg / ml versus  $5.6 \pm 0.6$  pg / ml in the control,  $P < 0.001$ ).



**Fig 1: The level of cytokines in the examined children, (pg / ml)**

It is known that TNF $\alpha$  is a pluripotent cytokine, which is mainly produced by monocytes and macrophages and performs the most important functions. During the onset of inflammation, it activates the endothelium, increases the expression of adhesion molecules on endothelial cells and promotes the adhesion of leukocytes to the endothelium, activates leukocytes (granulocytes, monocytes, lymphocytes), induces the production of other pro-inflammatory cytokines that have a synergistic effect with TNF $\alpha$ .<sup>[2,3]</sup> According to our analyzes in chronic bronchitis, a significant increase in the content of tumor necrosis factor- $\alpha$  was observed.

Attention was drawn to the nature of the synthesis of IL-4 in the examined sick children. As is known, IL-4 causes the differentiation of lymphocytes into T-helpers, proliferation and differentiation of B-lymphocytes. It has

a diverse and ambiguous effect on T-lymphocytes and monocytes. In our studies in sick children, a significant increase in IL-4 was recorded ( $P < 0.001$ ). An imbalance of cytokines is one of the causes of chronic inflammation. Literature data indicate that pathogens can have a multidirectional effect on the production of various cytokines. Most often, their immunosuppressive effect is expressed in a decrease in the level of interferons and in increased production of the anti-inflammatory cytokine IL-4. Participation in the inflammatory process of interferons (IFN $\gamma$  and IFN $\alpha$ ) is determined by their biological effects. IFN $\alpha$  activates natural killer cells, inhibits the reproduction of viruses and cell proliferation. IFN $\gamma$  activates the production of pro-inflammatory cytokines.

Thus, the examined children with chronic bronchitis develop secondary immunological deficiency, which is the basis for the use of drugs with immunocorrective effect.

Combined therapy with the inclusion of the antiviral and immunocorrecting drug Bioflazid after 1 month led to a

significant correction of the levels of the studied cytokines (Table 1), with more pronounced dynamics observed relative to interferon- $\gamma$  ( $P < 0.01$ ). As can be seen from the data in table 1, a positive trend was observed with respect to TNF $\alpha$  ( $P < 0.05$ ) and IL-4 ( $P < 0.01$ ). However, the values of the studied cytokines were significantly lower than the control data.

**Table 1: Dynamics of studied cytokines as a result of immunocorrective therapy in children with chronic bronchitis, ( $M \pm m$ ).**

Cytokines, pg / ml	Control group n=18	Before treatment	Traditional treatment+ Bioflazide After 1 month	Traditional treatment+ Bioflazid + Ribomunil After 3 months
TNF $\alpha$	14,5 $\pm$ 0,7	43,2 $\pm$ 1,8*	32,8 $\pm$ 1,5* **	18,5 $\pm$ 1,3 **
IFN $\gamma$	17,8 $\pm$ 1,0	9,4 $\pm$ 0,8*	13,7 $\pm$ 1,1* **	15,8 $\pm$ 1,2 **
IL-4	5,6 $\pm$ 0,6	15,9 $\pm$ 1,2*	12,8 $\pm$ 1,0* **	6,3 $\pm$ 0,9 **

Note: \* Values are significant relative to the control group.

\*\* Values are reliable in relation to the group before treatment ( $P < 0.05 - 0.001$ )

An analysis of the results after 3 months in the group of children to whom Ribomunil was connected to the complex therapy with Bioflazid showed the positive dynamics of not only the clinical parameters, but also the studied parameters of the immune system.

Thus, the use in the complex therapy of the antiviral drug Bioflazide and the drug Ribomunil, which has immunocorrecting activity, induce structural changes in the state of the immune system and thereby lead to a decrease in the incidence rate; decrease in the number of children belonging to the group of often and long-term sick; reducing the duration and alleviating the severity of the disease, almost no side effects. The ability to have an activating effect on various types of immunity (innate and adaptive immune response) allows us to consider this complex effective today with a multidirectional mechanism of action.

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