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Immunorehabilitation of convalescents after community-acquired pneumonia associated with bronchial obstruction syndrome

Key words: *community-acquired pneumonia, bronchial obstruction, cellular immunity, immunorehabilitation.*

According to WHO community acquired pneumonia (CAP) occupies one of the leading places by its morbidity and mortality, including population of working age. In addition, an increase in the frequency of pneumonia with complicated duration, which is associated with changes in the etiologic spectrum of pathogens, reduced immune defence, presence of comorbid pathology has been noticed in recent years. These peculiarities of pneumonia condition substantial economic losses from temporary disability of patients [3, 5, 10, 11].

Changes in the clinical duration of pneumonia are associated also with increasing of the frequency of bronchial obstruction formation [1, 5, 6]. Significant disturbances of ventilation function of lungs, which are often recorded in patients with CAP may have negative prognostic significance for the further development of broncho-pulmonary system' chronic diseases [9], which determines the necessity for recovery treatment.

However, clinical course and consequences of pneumonia are largely determined by the immune reactivity of the organism [5–7]. Immune disturbances may precede the development of pneumonia, may be intensified during their active course and be the basis for further development of broncho-pulmonary system's chronic diseases. Therefore, the success of treatment of this disease is not only a prescription of antibacterial treatment and correction of ventilation's disfunction, but also in the use of measures to strengthen the defensive reactions of the organism on the recovery phase of the disease [2].

It should be noted that according to computer tomography with high resolution, the full recovery after a course of antibiotics is observed only in 28,5 % of cases [8]. Special attention should be paid to the recovery treatment in convalescents after CAP with concomitant bronchial obstruction as they can be a risk group for further formation of asthma or chronic obstructive pulmonary disease.

The aim: development of complex immunorehabilitation' principles for convalescents after CAP associated with bronchial obstruction on the base of artificial rock salt medium usage (haloaerosoltherapy – HAT).

Materials and methods

Studies conducted in 38 patients with non-severe CAP, including 20 (52,6 %) women and 18 (47,4 %) men aged from 21 to 65 years, the average age of the patients – 44,8 ± 2,64 years. All patients after completion of antibiotic therapy in the hospital were directed to GI SPTC «Rehabilitation» for a course of recovery treatment. The diagnosis was established on the basis of characteristic epidemiological, clinical, X-Ray and laboratory data.

The function of lungs was performed using microprocessor system «Cardio+» (Ukraine). The severity of bronchial obstruction was determined by the value of forced expiratory volume in the first second (FEV_1) and the level of bronchial obstruction. In all patients the value of FEV_1 was less than 80 %, on average 70,9 ± 1,20 %.

Cellular immunity was studied before and after recovery treatment by the method of indirect immunofluorescence. We used five types of monoclonal antibodies, namely $CD3^+$, $CD4^+$, $CD8^+$, $CD22^+$, $CD16^+$. Such spectrum of investigations made it possible to analyze five calculated indices: 0-lymphocytes, the ratio of $CD4^+/CD8^+$, ratio of T-lymphocytes to B-lymphocytes ($CD3^+/CD22^+$), the ratio of T- and B-lymphocytes to 0-cells ($CD3^+ + CD22^+$)/0-

lymphocytes) and the sum of the above mentioned indexes (Σ), which make it possible to characterize the relationship between key populations and subpopulations of lymphocytes [4]. In addition, a complex of laboratory examinations was accomplished in the control group of healthy persons (21 individuals).

Methods of parametric and nonparametric statistical variation of the standard series were used for the statistical analysis of the received data. The validity of differences between the relative frequencies were calculated by the Student t-test. The average difference was considered as significant at $p < 0,05$. For calculations the Software STATISTICA 5.5 (company StatSoft, USA) was used.

For the treatment of convalescents after CAP three treatment complexes (TC) were used, the main component of which was the usage of artificial rock salt medium – haloaerosoltherapy (HAT). During the adaptation period (1–2 days), patients were undergone clinical, functional and laboratory examination. The period of adaptation to the haloaerosol was 3–4 days, during which the haloaerosol procedures' duration was increased from 15 to 60 minutes (15 min, 30 min, 45 min and 60 min). According to the TC-1 (basic TC) the main therapeutic period included daily HAT sessions lasting 60 minutes each (except Sundays). The treatment course consisted of overall 20–22 sessions of HAT.

According to the TC-2 (with increased haloaerosol intensity) the daily session of HAT was conducted in 2 stages of 30 minutes each with an interval between them in 3–4 hours, in freshly-formed aerosol medium, which promoted the increase in the total concentrations of active haloaerosol, especially particles of 4–10 microns in size.

The regime of haloaerosol procedures in TC-3 was similar to the TC-2. However, to improve the imunorehabilitative influence, it was combined with the usage of ukrainian natural immunomodulator derived from lactic acid bacteria Lactobacillus delbruesckii - blastolen (Blastomunil), which was administered by intramuscular injections of 0,6 mg every 5 days (that is overall 3 injections were contained 1,8 mg of blastolen per treatment).

Results and Discussion

The convalescents after CAP associated with bronchial obstruction were examined immediately after completion of antibiotic therapy. A significant decrease in the percent of mature T-lymphocytes ($52,8 \pm 0,76$ % at a normal value of $65,8 \pm 0,49$ %; $p < 0,001$) was revealed. This decrease was mainly on the expense of helpers subpopulation ($28,3 \pm 0,46$ % at a normal level of $37,3 \pm 0,43$ %; $p < 0,001$), although the percentage of $CD8^+$-lymphocytes was also reduced ($24,4 \pm 0,43$ % at a normal value of $27,2 \pm 0,39$ %, $p < 0,001$). Simultaneously, there was significant reduction in the ratio of $CD4^+/CD8^+$ ($1,17 \pm 0,02$ at a normal rate of $1,36 \pm 0,02$; $p < 0,01$). This shows the overwhelming deficit of $CD4^+$-cells' subpopulation and insufficiency of cellular immunity in general, which creates an additional risk for opportunistic infection development [6].

The number of 0-lymphocytes was increased in 1,5 times ($29,9 \pm 0,82$ % at a normal rate of $20,0 \pm 0,78$ %; $p < 0,001$), probably due to increased migration of highly differentiated cells into the inflammatory focus and growth of the percentage of functionally disabled lymphocytes in the peripherial blood. This fact indirectly points to the considerable intensity of inflammation and intense functioning of T-immunity, which is leading to the disturbances in T-lymphocytes' differentiation.

Thus, revealed changes of tested immunological indices confirm the incomplete end of the inflammation process in this group of patients, despite a course of antibacterial therapy. At the same time, the low percent of $CD3^+$-, $CD4^+$-cells and the ratio $CD4^+/CD8^+$ in patients with CAP indicates a certain exhaustion of immune system's function and its inability to form an adequate immune response to antigenic stimulus, which may contribute to the further chronization of inflammation in the broncho-pulmonary system.

Simultaneously, the level of B-lymphocytes was significantly higher compared to its value in the healthy subjects ($17,2 \pm 0,49$ % at a normal rate of $14,2 \pm 0,39$ %; $p < 0,001$), indicating some activation of humoral immunity due to the need of enhanced antibody production.

The calculated indexes $CD3^+/CD22^+$, $(CD3^+ + CD22^+)/0$-lymphocytes and the sum of relations (Σ) were significantly lower than in healthy due to the disturbances in the relationships and imbalance between populations of immune cells, which developed due to the decrease of T-lymphocytes level on the background of B- and 0-lymphocytes number elevation.

Natural killers – population of lymphocytes, which together with other factors of nonspecific resistance form the first line of defence against infectious agents, in particular, are active against cells infected by viruses. Significantly lower levels of $CD16^+$-lymphocytes compared with the healthy persons ($12,6 \pm 0,45$ % against $18,2 \pm 0,41$ % respectively, $p < 0,001$) were revealed in the group of examined patients with CAP. This was leading to an inadequate realisation of spontaneous and antibody-dependent cytotoxicity and to the disorders of immune defence.

Thus, the pronounced changes in T- and B-lymphocytes, their subpopulations and NK-cells were remained in patients with CAP after completion the basic medical treatment first of all antibacterial. These disturbances indicate the persistence of immune dysfunction and serve as a pathogenetic basis for the necessity of immunorehabilitative measures in patients with CAP in order to provide normal functioning of the immune system, strengthening protective reserves of the organism and prevent the development of chronic inflammation.

The usage of HAT, on the whole, has a positive effect at the convalescents after CAP with symptoms of bronchial obstruction, which resulted in a significant decrease of the frequency or disappearance of residual clinical manifestations after the acute period of the disease and elevation of ventilation indices due to the pronounced sanative effect of haloaerosol and increased bronchial drainage function. In addition, an improvement of cellular immunity indices was found (table 1).

In particular, a significant increase in the number of T-lymphocytes and helpers' subpopulation, NK-cells, of the ratio $CD3^+/CD22^+$ and the sum of indexes was found under

the influence of TC-1. At the same time, there has been a downward trend in the number of B-lymphocytes and 0-lymphocytes, which is probably a result of attenuation of the residual manifestations of inflammation under the influence of HAT and indicates a certain trend to the normalization of cells differentiation and subsequent immune response.

Nevertheless, the levels of most of the studied parameters that characterize T-immune system (CD3$^+$-, CD4$^+$-, CD8$^+$-lymphocytes, CD4$^+$/CD8$^+$), and the number of NK-cells remained significantly lower than in the control. At the same time, the number of 0- and B-lymphocytes was significantly higher against the control, suggesting the preservation of secondary T-cell imbalance and deficient immunomodulatory effectiveness of TC-1, as the number of active mature T-cells capable of immediate immune response remained low.

At Patients Treated By Tc-2 (Table 1) Significant Improvements Of Almost All Studied Parameters (Except The Number Of Cd8$^+$-Lymphocytes) Were Observed, Which Indicates The Growth Of Sufficiency Of The Immune Defence System Of The Organism.

Table 1

Changes in the cellular immunity in convalescents after CAP under the influence of recovery treatment

Indices and their units	Control (n = 21)	Treatment complexes		
		TC-1 (n = 14)	TC-2 (n = 12)	TC-3 (n = 12)
CD3$^+$, % p p'	65,8±0,49	52,8±1,48** 57,2±1,42** <0,05	53,3±1,21** 61,5±1,06** <0,001 p$_{1-2}$<0,05	52,4±1,29** 64,8±1,14 <0,001 p$_{2-3}$<0,05
CD22$^+$, % p	14,2±0,39	17,4±0,68** 16,1±0,59** <0,2	17,4±0,94** 15,4±0,72* <0,1	16,9±0,99** 15,2±0,49* <0,2
0- lymphocytes, % p p'	20,0±0,78	29,9±1,64** 26,7±1,24** <0,2	29,3±1,06** 23,1±0,86** <0,001 p$_{1-2}$<0,05	30,7±1,48** 20,0±0,91 <0,001 p$_{2-3}$<0,05
CD4$^+$, % p p'	37,3±0,43	28,4±0,84** 31,6±1,05** <0,05	28,7±0,69** 34,6±0,63** <0,001 p$_{1-2}$<0,05	28,0±0,88** 36,8±0,65 <0,001 p$_{2-3}$<0,05
CD8$^+$, % p	27,2±0,39	24,3±0,79** 25,5±0,58** <0,3	24,6±0,72** 26,0±0,46** <0,2	24,3±0,76** 26,8±0,55 <0,02
CD4$^+$/CD8$^+$ p p'	1,36±0,02	1,18±0,03** 1,24±0,04** <0,2	1,17±0,03** 1,33±0,03 <0,001 p$_{1-2}$<0,05	1,16±0,05** 1,38±0,03 <0,01 p$_{2-3}$<0,3
CD3$^+$/CD22$^+$ p	4,41±0,15	3,09±0,15** 3,65±0,20** <0,05	3,19±0,23** 4,10±0,23* <0,01	3,23±0,22** 4,34±0,19 <0,001
CD3$^±$+CD22$^±$ 0-lymphocytes p p'	4,01±0,18	2,49±0,20** 2,86±0,19** <0,2	2,48±0,14** 3,40±0,17** <0,001 p$_{1-2}$<0,05	2,35±0,16** 4,11±0,23 <0,001 p$_{2-3}$<0,02
Σ of ratios p p'	10,1±0,21	6,77±0,28** 7,75±0,36** <0,05	6,84±0,25** 8,83±0,30** <0,001 p$_{1-2}$<0,05	6,74±0,25** 9,83±0,37 <0,001 p$_{2-3}$<0,05
CD16$^+$, % p'	18,2±0,41	12,1±0,66** 14,9±0,76** <0,01	13,1±0,84** 15,8±0,49** <0,01	12,8±0,91** 17,2±0,68* <0,001

Notes: 1. In the numerator – indices before treatment, in the denominator – indices after treatment;
2. * tendency to significant changes of indices compared with the control;
3. ** valuable changes of indices compared with the control;
4. p – probability of difference of indices before and after treatment; 5. p' - probability of difference of data after treatment between different TC.

Comparing the values of the studied parameters after treatment it was noted that under the influence of TC-2, compared with the TC-1, there was a significant increase in the number of $CD3^+$-lymphocytes, helpers' subpopulation, ratios $CD4^+/CD8^+$, $(CD3^++CD22^+)/0$-lymphocytes and the sum of calculated indexes and reduction of the number of 0-lymphocytes. These results indicate a more complete correction of immune dysfunction in the group of patients treated according to the TC-2 probably as a result of eliminating residual inflammatory manifestations and grounded by a pronounced anti-inflammatory and sanative influence of two daily treatment sessions of haloaerosol.

However, it should be noted that even when using TC-2 the levels of $CD3^+$-, $CD4^+$- $CD8^+$-lymphocytes, the ratio $(CD3^++CD22^+)/0$-lymphocytes and the sum of indexes remained significantly lower than in the control, indicating residual T-cellular insufficiency.

At the same time, under the influence of TC-3 (combination of HAT with high haloaerosol intensity and intramuscular injections of immunomodulator blastolen) the immune correcting effect of recovery treatment was more pronounced compared to the TC-2. Normalization of the most of studied immune indices were observed in convalescents after CAP (table 1), which may indicate complete inhibition of the inflammation process, normalization of T-lymphocytes' system and creation of conditions for its further physiologic function.

Thus, the usage of various regimes of HAT in recovery treatment of convalescents after CAP associated with bronchial obstruction leads to a significant improvement of the cellular immunity function, but complete normalization of some of the studied parameters (number of $CD3^+$-, $CD4^+$-lymphocytes, NK-cells, the sum of indexes) was not reached that determines the necessity for a comprehensive treatment complex administration with additional use of immunomodulatory medication.

Conclusions

1. Recovery treatment based on HAT usage leads to the improvement of the effectiveness of treatment at convalescents after CAP with the presence of bronchial obstruction, as evidenced by a significant improvement in the indices of cellular immunity.

2. Expressiveness of positive changes in cellular immunity in convalescents after CAP with concomitant bronchial obstruction depends on the haloaeroltherapy regime and is significantly better after TC-2 with high intensity of haloaerosol influence.

3. Usage of only non-pharmacological treatment based on HAT for rehabilitation of convalescents after CAP associated with bronchial obstruction syndrome does not provide a complete normalization of some cellular immunity indices, which determines the necessity of a complex treatment with the additional administration of immunomodulators.

4. Usage of TC-3 (with high intensity of haloaerosol and additional intramuscular injections of immunomodulator blastolen) is the most effective in convalescents after CAP, leading to the normalization of cellular immunity and creating conditions for preventing chronic bronchial obstruction.

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ИММУНОРЕАБИЛИТАЦИЯ РЕКОНВАЛЕСЦЕНТОВ ПОСЛЕ ВНЕБОЛЬНИЧНЫХ ПНЕВМОНИЙ С СОПУТСТВУЮЩИМ БРОНХООБСТРУКТИВНЫМ СИНДРОМОМ

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Резюме

Цель исследования – *разработать принципы комплексного иммунореабилитационного лечения реконвалесцентов после внебольничных пневмоний (ВП) с сопутствующим бронхообструктивным синдромом на основе использования искусственных аэрозольных сред каменной соли (галоаэрозольтерапии – ГАТ).*

Объект исследования: *38 реконвалесцентов после ВП нетяжелого течения с бронхообструктивным синдромом (ОФВ$_1$ < 80 %) и 21 практически здоровый человек в качестве лабораторного контроля.*

Методы исследования: *клинико-функциональные, непрямой иммунофлюоресцентный метод фенотипирования лимфоцитов с помощью моноклональных антител (CD3$^+$, CD22$^+$, CD4$^+$, CD8$^+$, CD16$^+$), статистические.*

Результаты. *У реконвалесцентов после ВП после завершения антибактериальной терапии выявлены достоверные изменения количества Т-, В-лимфоцитов и натуральных киллеров, которые свидетельствуют о сохранении иммунной дисфункции и служат патогенетическим основанием для проведения иммунореабилитационных мероприятий. Применение ГАТ способствовало*

повышению эффективности лечения реконвалесцентов после ВП. Это подтверждалось существенным улучшением показателей клеточного иммунитета, выраженность которого зависела от режима проведения ГАТ и была достоверно лучше при повышенной интенсивности галоаэрозольного воздействия. Однако применение только немедикаментозного лечения не обеспечивало нормализации ряда показателей клеточного иммунитета. В то же время, сочетание повышенной интенсивности галоаэрозольного влияния и внутримышечно введения иммуномодулятора бластолена способствовало полному его восстановлению.

Выводы. *У реконвалесцентов после ВП наиболее эффективным является применение лечебного комплекса с повышенной интенсивностью галоаэрозольного воздействия и дополнительным внутримышечным назначением иммуномодулятора бластолена, что ведет к нормализации показателей клеточного иммунитета и создает предпосылки для предотвращения возникновения хронической бронхообструктивной патологии.*

Ключевые слова: *внегоспитальные пневмонии, бронхообструкция, клеточный иммунитет, иммунореабилитация.*

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IMMUNOREHABILITATION OF RECONVALESCENTS AFTER COMMUNITY-ACQUIRED PNEUMONIA ASSOCIATED WITH BRONCHIAL OBSTRUCTION SYNDROME

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Summary

The aim: *development of complex immunorehabilitation' principles for convalescents after community acquired pneumonia (CAP) associated with bronchial obstruction on the base of artificial rock salt medium usage (haloaerosoltherapy − HAT).*

The object of study: *38 convalescents after non-severe CAP associated with bronchial obstruction (FEV$_1$ < 80 %) and 21 healthy individuals as a laboratory control.*

Methods: *clinical and functional methods of examination, indirect immunofluorescence method of lymphocytes' phenotyping using monoclonal antibodies (CD3$^+$, CD22$^+$, CD4$^+$, CD8$^+$, CD16$^+$), statistical analysis.*

Results. *Statistically significant disturbances in the levels of T-, B-lymphocytes and natural killer cells were found at convalescents after non-severe CAP after medicamental treatment. These changes indicate a persistence of immune dysfunction and are a pathogenetic basis for the necessity of immunorehabilitative measures. Use of haloaerosoltherapy contributed to the improving the effectiveness of treatment of convalescents after CAP with bronchial obstruction. This effect was confirmed by considerable improvement of cellular immunity indices, the expressiveness of which depended on the haloaerosoltherapy regimes and was significantly better when high intensity of haloaerosol influence was used. However, the use of non-pharmacological treatment based on haloaerosoltherapy didn't provide normalization of all tested cellular immunity indices. At the same time, combination of high intensity haloaerosol influence and intramuscular injections of immunomodulator blastolen promoted complete recovery of cell-mediated immunity.*

Conclusion. *The usage of medical complex with high intensity of haloaerosol influence with additional intramuscular prescription of immunomodulator blastolen appeared to be the most effective at convalescents after CAP. It leads to the normalization of cellular immunity and creates conditions for the prevention of chronic bronchial obstruction.*

Key words: *community-acquired pneumonia, bronchial obstruction, cellular immunity, immunorehabilitation.*

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