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VARIOUS ORIGINS PNEUMONIA EXPRESS DIAGNOSIS DURING THE WAR IN UKRAINE

Oleh M. Koliada¹, Lyudmila M. Tynnyka², Tetiana I. Koliada³, Andrii Yu. Nikolchenko², Yevgen I. Legach⁴, Vyacheslav Yu. Globa⁴, Sergiy Ye. Legach¹

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Summary

Introduction. The study of the serum level of PCT and sTREM has been proposed as markers of bacterial infection, which have been applied for the early differentiation of processes of viral and bacterial etiology.

Aim. Determination of express markers for predicting the effectiveness of empiric antibiotic therapy in patients with IPD.

Materials and methods. Study groups with viral pneumonias, as well as bacterial etiology caused by *Haemophilus influenzae*, groups of patients with ChOPd I-II III-IV stages were formed. Controls for the studied groups were patients at the stage of remission and a group of healthy individuals without lung pathology and infectious diseases. The specific identification of microorganisms in the clinical material of patients with pneumonia was carried out in two stages: the first stage in the laboratories of the respective hospitals was carried out by the method of HIR and CFT; the second was carried out with the help of specific antibodies by the indirect fluorescence method using a fluorescent microscope and qualitative analysis test kits («Respiratory Tract Profile 1 BIOCHIP Mosaics for infectious serology», Medizinische Labordiagnostika AG «EUROIMMUN»).

Results. In our study, the serum level of sTREM-1 was used as a criterion for assessing the probability of bacterial infection and, accordingly, increasing the degree of reliability of the prognosis provided by the PCT level study. The expression level of sTREM-1 and PCT were used as markers of bacterial infection for the early differentiation of processes of viral and bacterial etiology.

Conclusions. The study of serum levels of PCT and sTREM, which are markers of bacterial infection and are used for early differentiation of processes of viral and bacterial etiology, has demonstrated the prognostic importance of the express assessment method of the infectious process etiology. The obtained results were used in the development of method for predicting the effectiveness of empiric antibiotic therapy in patients with IPD infectious diseases.

Keywords: chronic obstructive pulmonary disease, procalcitonin, soluble triggering receptor expressed on myeloid cells

INTRODUCTION

There is no standard for microbiological infections diagnosis of inflammatory pulmonary diseases (IPD) today, especially in war conditions in Ukraine, since the results of microbiological studies in a significant part of cases are not reliable, especially in patients with chronic inflammatory diseases of the distal respiratory tract,

accompanied by intensive colonization of the respiratory tract with commensal and opportunistic microflora. Traditionally, C-reactive protein (CRP) and interleukin-6 are used as markers of inflammation, however, the level of specificity of these indicators, due to the extremely wide range of inducers (and these are almost all inflammatory mediators), allows for high-quality differential diagnosis only between inflammatory and non-inflammatory

infiltrates in the lungs [1, 3, 4]. The possibilities for differential etiological diagnosis of bacterial and viral pneumonia in the early stages of the disease are quite limited, primarily due to the low level of information content of bacteriological methods of IPD diagnosis. In case of pneumonia, they are actually excluded from modern clinical practice during the war in Ukraine, which justifies the relevance of searching for additional criteria useful in determining of the etiotropic therapy. Taking this into account, the study of effective markers suitable for early differential diagnosis of bacterial and viral infections of IPD is relevant at the present time.

In connection with it, new markers for differentiating the bacterial and non-bacterial nature of IPD, which include procalcitonin (PCT) and sTREM (Soluble Triggering Receptor Expressed on Myeloid cells) have been proposed for investigation.

AIM

Determination of express markers for predicting the effectiveness of empiric antibiotic therapy in patients with IPD.

The tasks of the article:

1. Investigation of serum PCT and sTREM levels for early differentiation of processes of viral and bacterial etiology. 2. Determination of PCT and sTREM levels, which are specific for certain forms of IPD. 3. Evaluation of the possibility of using express markers to predict the etiology and course of chronic inflammatory pulmonary diseases in order to ensure the effectiveness of antibiotic therapy.

MATERIALS AND METHODS

Patients (442 persons) with acute pneumonia who were treated in the therapeutic department of the Communal Non-profit Organization «Prof. O. I. Meshchaninov's Municipal Clinical Hospital of Emergency Medical Care of the Kharkiv Regional Council» and «Kharkiv Regional Clinical Infectious Disease Hospital» were examined. The diagnosis of chronic obstructive pulmonary disease ChOPd was formulated based on the materials of the Order of the Ministry of Health No. 128 of March 19, 2007 [2]. The study groups with viral pneumonia were formed from groups of patients with ChOPd stages I-II RvIa (n=68), with ChOPd stages III-IV RvIIa (n=51). A group of 91 patients with ChOPd at the stage of remission RvChOPd (n=91) was formed as a control for the study groups RvIa and RvIIa. The study groups with pneumonia of bacterial etiology caused by Haemophilus influenzae were formed from groups of patients with ChOPd stages I-II HiIb (n=54), with ChOPd stages III-IV HiIIb (n=63). A group of 115 patients with ChOPd at the remission stage of

HiChOPd (n=115) was formed as a control for the study groups HiIb and HiIIb respectively. The Control group (C) was formed from healthy individuals without pulmonary pathology and infectious diseases (C, n=24).

Specific identification of Influenza virus type A, Influenza virus type B, Adenovirus, Parainfluenza virus type 1, Parainfluenza virus type 2, RSV, Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae in the clinical material of patients with pneumonia was carried out in two stages: the first stage in the laboratories of the respective Hospitals was carried out by the method of HIR (reaction of indirect hemagglutination) and CFT (complement fixation test); the second was carried out with the help of specific antibodies by the indirect fluorescence method using a fluorescent microscope and qualitative analysis test kits («Respiratory Tract Profile 1 BIOCHIP Mosaics for infectious serology», Medizinische Labordiagnostika AG «EUROIMMUN»). The bacterial infection marker sTREM was assessed by enzyme-linked immunosorbent assay using a specialized sTREM ELISA test system. The manufacturer is IQ Products, the Netherlands [3]. For rapid diagnosis of PCT, a semi-quantitative immunochromatographic method of determining the concentration of procalcitonin in plasma or blood serum was used using a test system (BRANMS PCT-Q) [1, 4]. Comparison of sTREM results between groups was performed using the Mann-Whitney U test. Comparison of sTREM between consecutive days of the study (1st, 2nd and 3rd days) was carried out using the Wilcoxon T test. Statistical processing of the obtained data was carried out using the programs STATISTICA 11.0 (StatSoft, Inc) and XLSTAT 19.6 (Addinsoft). The Mann-Whitney U-test and Fisher's exact test were used to determine reliable differences between indicators in the studied samples, and the Student's t-test was used for normal distribution [5].

RESULTS AND DISCUSSION

The dynamics of PCT and sTREM indicators against the background of viral and bacterial pneumonia on the 1st, 2nd and 3rd days of the course of ChOPd in patients of all studied groups RvIa (n=68), RvIIa (n=51), HiIb (n=54), HiIIb (n=63), RvChOPd (n=91), HiChOPd (n=115), which did not change during the three-day period ($p < 0.05$) were determined in our work. Therefore, our work presents the dynamics of changes in the average level of PCT and sTREM in the blood serum of patients with different ChOPd courses in comparison with the control group and ChOPd in the remission stage, which were mediated by viral and bacterial factors.

The results of the study of the PCT level in the blood serum of patients with pneumonia caused by viral and bacterial (H. influenzae) infection against the background of ChOPd are shown in fig. 1.

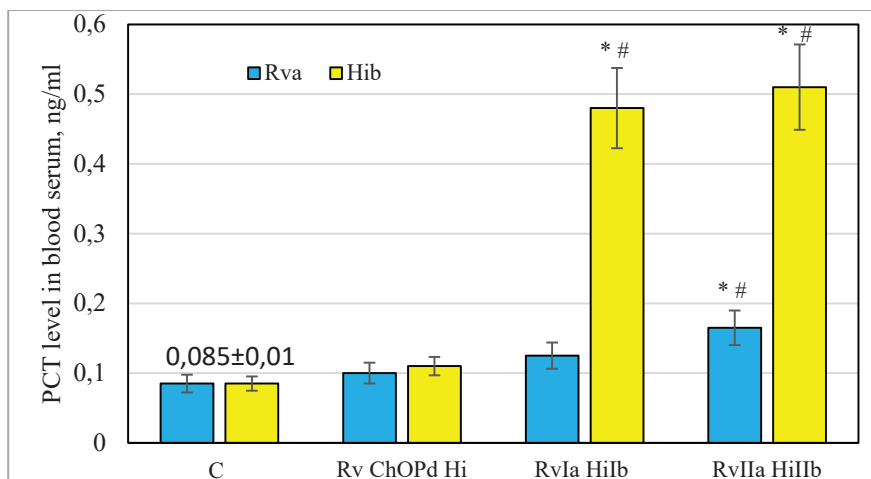


Figure 1. Level of PCT in blood serum of patients with pneumonia caused by viral and bacterial infection in the background of ChOPd; (* – the difference is significant in comparison with control group (C), $p < 0.05$; # – the difference is significant in comparison with ChOPd group in the remission stage, $p < 0.05$).

According to the data obtained (fig. 1), the average PCT level in the blood serum of patients against the background of bacterial factors (*H. influenzae*) was significantly increased, almost 6 times, in patients with a severe course of ChOPd (group HiIb 0.48 ± 0.06 ng/ml, HiIIb 0.51 ± 0.08 ng/ml) compared to the control (C) group (0.08 ± 0.01 ng/ml) and 5 times compared to the HiChOPd group (0.11 ± 0.02 ng/ml) at the remission stage, respectively. A significant increase in the PCT level in the blood serum compared to the control and the group in the remission stage of RvChOPd was observed only in patients with severe stages of ChOPd RvIIa (0.16 ± 0.02 ng/ml) against the background of viral pneumonia. At the same time, no significant differences were noted between the control group and the groups at the remission stage (RvChOPd and HiChOPd). It is known [1, 4] that under physiological conditions PCT is produced exclusively by C cells of the thyroid gland. PCT normal serum concentration is within 0.01-0.1 ng/ml, however, against the background of severe bacterial infections and some other forms of inflammation, the expression of this protein is observed in neuroendocrine cells of a number of parenchymal organs and tissues (lungs, liver, adrenal glands, pancreas). This expansion of PCT producers' substances is accompanied by a rapid and steady growth of its level tenfold. The mechanism of such induction during the development of the infectious process can occur both directly under the influence of bacterial endotoxins, lipopolysaccharides and indirectly – under the influence of mediators of the humoral or cellular immune response. It is known [1, 4, 5] that a conclusion about absence of bacterial infection and the impracticality of starting or continuing the course of antibiotic therapy is given at the value of $PCT < 0.1$ ng/ml; antibiotics may be prescribed to patients in critical condition; if an antibiotic has already been prescribed, then if the PCT level remains less than 0.1 ng/ml ($PCT < 0.1$ ng/ml), the course is prematurely stopped 1-3 days after its start. A conclusion about the low probability of a bacterial

infection is made at PCT value in the range of 0.1-0.25 ng/ml; antibiotics may be prescribed to patients belonging to the high-risk group; if an antibiotic is prescribed, an early interruption of the course is indicated, provided there is no increase in the PCT level.

The results obtained in our work regarding the level of PCT in the group with severe ChOPd RvIIa (0.16 ± 0.02 ng/ml) against the background of viral factors indicate the impracticality of using antibiotic therapy and the likelihood of using immunocorrective therapy. A PCT level in the range of 0.25-0.5 ng/ml indicates the probable presence of a bacterial infection and the feasibility of starting or continuing antibiotic therapy. A PCT level > 0.5 ng/ml is regarded as a marker of the bacterial infection and a well-defined indication for starting or continuing a course of antibiotic therapy. The obtained results regarding the level of serum PCT in groups with a severe course of ChOPd against the background of bacterial factors (groups HiIb 0.48 ± 0.06 ng/ml, HiIIb 0.51 ± 0.08 ng/ml) are consistent with the data on the feasibility of prescribing or continuing the course of antibiotic therapy. In our investigation, the serum level of sTREM-1 was used as a criterion for assessing the probability of bacterial infection and, accordingly, increasing the degree of reliability of the prognosis provided by the PCT level study. The expression level of sTREM 1 and, accordingly, the serum concentration of sTREM-1 increase rapidly and significantly in bacterial and viral infections, as well as in non-infectious inflammatory diseases, including ChOPd. The most pronounced increase is observed when a bacterial infection is added to the existing aseptic inflammatory process and against the background of the development of the systemic inflammatory response syndrome (SIRS). At the same time, there are published research results [3, 6, 7] indicating a significantly lower level of this indicator against the background of infections caused by viruses compared to infections caused by bacteria.

The investigation of the sTREM level in blood serum (fig. 2) revealed its sharp increase, 46 times, in patients with a stable course of RvChOPd (11.50 ± 1.22 pg/ml),

HiChOPd ($11,10 \pm 1,21$ pg/ml) compared to controls (0.25 ± 0.04 pg/ml) both against the background of viral and bacterial factors.

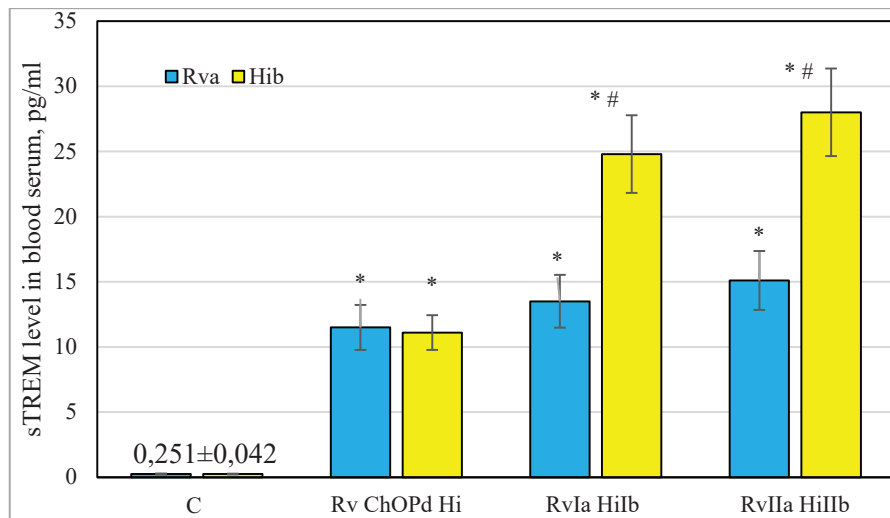


Figure 2. Level of sTREM in blood serum of patients with pneumonia caused by viral and bacterial infection in the background of ChOPd; (* – the difference is significant in comparison with control group (C), $p < 0.05$; # – the difference is significant in comparison with ChOPd group in the remission stage, $p < 0.05$).

Whereas, the investigated indicator increased almost 100 times in the blood serum of patients with severe ChOPd stage I-II and stage III-IV (groups HiIb $24,81 \pm 2,69$ pg/ml, HiIIb $28,01 \pm 3,01$ pg/ml) compared to the control group (C) on the background of ChOPd caused by *H. influenzae*. At the same time, the serum level of sTREM in the groups with a severe course of ChOPd HiIb stage I-II and HiIIb stage III-IV increased by 2.2 and 2.5 times, respectively, compared to the group HiChOPd during the remission period precisely against the background of bacterial factors. As for the influence of viral factors, the studied indicator does not reliably distinguished in groups with different courses of ChOPd RvIa ($13,50 \pm 1,36$ pg/ml) RvIIa ($15,10 \pm 1,60$ pg/ml) in comparison with the disease in the remission stage of RvChOPd ($11,50 \pm 1,22$ pg/ml). This indicates that the serum level of sTREM distinctly responds to the presence of IPD of any etiology by increasing this indicator compared to a control group of healthy patients. In addition, the dynamics of changes in the studied indicator demonstrate its significant increase in patients with severe and moderate ChOPd against the background of bacterial factors (groups HiIb and HiIIb), which indicates the possibility of detecting the disease in the early stages, differentiating its factors and correcting treatment tactics. While the serum level of PCT increases significantly only in patients with chronic ChOPd on the background of bacterial pneumonias (groups HiIb and HiIIb), which makes the prognostic value of this indicator impossible without taking into account the level of sTREM.

The level of PCT in the blood serum of patients with viral pneumonia on the background of ChOPd practically does not depend on the severity of the disease, with the exception of ChOPd stage III-IV, as it has been shown in the investigation. At the same time, a significant increase in the average level of PCT in groups with different degrees of ChOPd stage I-II and stage III-IV against the background of *H. influenzae* was demonstrated. On the basis of the obtained data, it was shown that the level of sTREM is the most sensitive indicator for early rapid diagnosis and treatment IPD tactics of viral and bacterial etiology, which is consistent with the results of the study [7], which consider sTREM not only the most valuable biomarker for the early diagnosis of pneumonia in children, who underwent heart surgery, and also the best prognostic key regarding treatment tactics. And at the same time, our work shows that the levels of sTREM and PCT have prognostic value as markers of early diagnosis of IPD caused by bacterial factors, which provides an opportunity to adjust treatment tactics. The method was tested in the clinical studies 'ProCAP' and 'ProRESP' [7], within which a 50 % reduction in the frequency of prescribing antibiotics was achieved in patients with inflammatory diseases of the lower respiratory tract in the group with low PCE levels. The positive qualities of the method include the fact that the laboratory procedure using a standard test system [3, 8] lasts less than 20 minutes, the results are available for analysis in an hour, which makes this indicator a very convenient tool for clinical express monitoring.

CONCLUSIONS

1. Among the pathogens isolated and identified by bacteriological methods, microorganisms were found to which an increase in serum antibodies was observed, which indicates a certain level of informativeness of the combination of these methods in cases where establishing the etiology is fundamentally important.

2. The study of serum levels of PCT and sTREM, which are markers of bacterial infection, demonstrated the possibility of their use for early differentiation of viral and bacterial etiology processes, as well as increasing the prognostic potential of the express method for assessing the etiology of the infectious process.

3. The obtained results were used in the elaboration of method for predicting the effectiveness of empiric antibiotic therapy in patients with IPD infectious diseases.

Prospects for further research: investigation of the mechanisms of realization of PCT and sTREM effects in inflammatory pulmonary diseases.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The study was approved by the Commission on Biomedical Ethics of State Institution «I. I. Mechnikov's Institute of Microbiology and Immunology of National Academy of Medical Sciences of Ukraine» (protocol No. 3 from 07.12.23) and was conducted in accordance with the written consent of the participants and in accordance with the principles of bioethics set forth in the Helsinki Declaration «Ethical Principles of Medical Research Involving Humans» and «General Declaration on Bioethics and human rights (UNESCO).»

FUNDING AND CONFLICT OF INTEREST

There is no conflict of interest. Source of funding is budget financing within the topic of the State Registration No. 0105U001112 «Clinical, immunological and microbiological aspects of the course and prognosis of inflammatory pulmonary diseases.»

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Резюме

ЕКСПРЕС-ДІАГНОСТИКА ПНЕВМОНІЙ РІЗНОГО ГЕНЕЗУ В УМОВАХ ВІЙНИ В УКРАЇНІ

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Вступ. Дослідження сироваткового рівню РСТ та sTREM було запропоновано як маркери бактерійної інфекції, які застосовано для ранньої диференціації процесів вірусної та бактерійної етіології.

Мета. Визначення експрес-маркерів для прогнозування ефективності емпіричної антибіотикотерапії у пацієнтів із запальними захворюваннями легень ЗЗЛ.

Матеріали та методи. Досліджувані групи з вірусними пневмоніями, а також бактеріальної етіології, викликаними *Haemophilus influenzae* було сформовано з групи пацієнтів з ХОЗЛ I-II, III-IV стадіями. Контролем для досліджуваних груп були пацієнти на стадії ремісії та група здорових осіб без легеневої патології та інфекційних захворювань. Специфічну ідентифікацію мікроорганізмів в клінічному матеріалі хворих на пневмонію проводили в два етапи: перший етап в лабораторіях відповідних стаціонарів методом РНГА та РЗК; другий – за допомогою специфічних антитіл методом непрямої флюоресценції із використанням люмінесцентного мікроскопу та тестових наборів якісного аналізу («Respiratory Tract Profile 1 BIOCCHIP Mosaics for infectious serology», Medizinische Labordiagnostika AG «EUROIMMUN»).

Результати. В проведеному нами дослідженні як критерій, що дозволяє оцінити вірогідність наявності бактерійної інфекції, та, відповідно, підвищити ступінь достовірності прогнозу, що забезпечується дослідженням рівня РСТ, використано сироватковий рівень sTREM-1. Рівень експресії sTREM-1 та РСТ були використані, як маркери бактерійної інфекції для ранньої диференціації процесів вірусної та бактерійної етіології, що продемонструвало можливість підвищення прогностичного потенціалу методу експрес оцінки етіології інфекційного процесу.

Висновки. Дослідження сироваткових рівнів РСТ та sTREM, які є маркерами бактерійної інфекції та використовуються для ранньої диференціації процесів вірусної та бактерійної етіології, продемонструвало можливість підвищення прогностичного потенціалу методу експрес-оцінки щодо етіології інфекційного процесу. Отримані результати використано при розробці способу прогнозування ефективності емпіричної антибіотикотерапії у пацієнтів з інфекційними захворюваннями ЗЗЛ.

Ключові слова: хронічне обструктивне захворювання легень, прокальцитонін РСТ, розчинний тригерний рецептор, експресований на міелоїдних клітинах sTREM