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## PROGNOSIS OF CELLULAR ENERGY METABOLISM SHIFTS IN ADOLESCENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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**Ключевые слова:** внебольничная пневмония, дети, клеточный энергетический метаболизм

**Abstract.** Prognosis of cellular energy metabolism shifts in adolescents with community-acquired pneumonia. Zubarenko O.V., Stoieva T.V., Koval L.I., Kopiyka G.K., Papinko R.M. Pneumonia is one of the most severe respiratory pathology forms in children, which contributes significantly to infant mortality. The high risk of chronic bronchopulmonary process and child's disability, in case of severe and complicated disease, requires careful pathophysiological change's analysis in community-acquired pneumonia (CAP) in children. In particular, for the prediction of these disorders in children with CAP are important the dysmetabolic phenomena study and the specific approaches development. The immediate aim of this work is to study the cellular energy metabolism (CEM) features and to develop approaches for the early bioenergetic disorders diagnostics in conditions of community-acquired pneumonia in adolescents. The aim of the study is to develop approaches for the early diagnosis of shifts in energy metabolism in children aged 14-18 years with CAP. An examination of 41 children aged 14-16 years with the definition of CEM indicators was conducted in order to develop an approach for predicting CEM disorders in community-acquired pneumonia using the method of logistic regression. A logistic regression method was used to develop a method for predicting CEM disorders in children with CAP. The characteristics of CEM in children with CAP were determined. A decrease in the succinate dehydrogenase activity and an increase in the lactate dehydrogenase / succinate dehydrogenase ratio in children with CAP relative to the reference parameters were observed, which indicated an inhibition of the anaerobic energy synthesis pathway. Two mathematical models for predicting CEM disorders in CAP based on logistic regression equations were proposed. The first mathematical model consisted of social and health characteristics and of pneumonia clinical course characteristics. In ROC analysis the area under the curve (AUC) was 0.82, diagnostic specificity – 71%, diagnostic sensitivity – 90%. The second model included only hematological parameters, AUC – 0.78, diagnostic specificity – 69%, diagnostic sensitivity – 81%. Thus, changes in CEM in children with CAP aged 14 – 18 years have been established. Two methods for predicting disorders of CEM in children with CAP have been developed, which can be applied to optimize the treatment of children with CAP aged 14-18 years.

**Реферат.** Прогнозування зсувів у клітинному енергетичному метаболізмі при позалікарняній пневмонії в дітей підліткового віку. Зубаренко О.В., Стосва Т.В., Коваль Л.І., Копійка Г.К., Папінко Р.М. Однією з найбільш тяжких форм респіраторної патології в дітей є пневмонія, що вносить істотну частку в дитячу смертність. Високий ризик хронізації бронхолегеневого процесу й інвалідизації дитини, у випадку тяжкого та ускладненого перебігу захворювання, вимагають ретельного аналізу патофізіологічних змін при позалікарняній пневмонії (ПП) у дітей. Зокрема, на часі є вивчення дизметаболических явищ та розробка специфічних підходів щодо прогнозу розвитку таких розладів при ПП у дітей. Метою роботи є дослідження особливостей клітинно-енергетичного метаболізму (КЕМ) та розробка підходів до ранньої діагностики біоенергетичних порушень за умов позалікарняної пневмонії в дітей підліткового віку. Проведено обстеження 41 дитини віком 14-18 років із визначенням показників КЕМ, для розробки способу прогнозування розладів КЕМ при ПП було застосовано метод логістичної регресії. Визначено характеристики КЕМ у дітей, хворих на ПП. Конста-

товано зниження активності сукцинатдегідрогенази та збільшення значення співвідношення лактат-дегідрогенази до сукцинатдегідрогенази при ПП відносно показників контрольної групи, що вказувало на пригнічення анаеробного шляху метаболізму. Запропоновано дві математичні моделі прогнозування розладів КЕМ при ПП на базі рівняння логістичної регресії. Перша математична модель складалась з анамнестичних даних, супутніх патологічних станів та характеристик клінічного перебігу ПП, при ROC-аналізі площа під кривою (AUC) становила 0.82, діагностична специфічність – 71%, діагностична чутливість – 90%. Друга модель включала в себе гематологічні показники, AUC – 0.78, діагностична специфічність – 69%, діагностична чутливість – 81%. Таким чином, встановлено наявність зрушення КЕМ при ПП у дітей віком 14-18 років, розроблено два способи прогнозування розладів КЕМ при ПП у дітей, що може бути застосовано для вдосконалення медичної допомоги підліткам із урахуванням індивідуальних особливостей організму.

Pneumonia is a common and potentially dangerous disease in pediatric patients. The study of community-acquired pneumonia (CAP) in the last decade has allowed to improve understanding of this problem in many respects and to optimize diagnostic and therapeutic approaches.

In spite of modern achievements in medical science, the CAP incidence remains high, requiring a further in-depth study of the body state and the disease pathogenic mechanisms investigation. Taking into consideration the complexity of pathophysiological processes in pneumonia, the undeniable fact today is that the classical clinical examination is insufficient for the accurate disease severity assessment [9].

Numerous studies indicate that there is an association between shifts in metabolic profile and depth of tissue damage due to inflammatory stress. Thus, identifying cellular energy metabolism (CEM) shifts can improve understanding of the pneumonia underlying pathophysiological mechanisms in children and develop new tactics for the CAP prevention and treatment. The above noted is extremely important in conditions of increasing antibiotic resistance and slow development of effective and safe antibiotics, that can be used in pediatrics [8]. A comprehensive study of metabolism shifts in pneumonia in children identified a number of biomarkers – L-histidine, hypoxanthine, glutamic and uric-acids, L-tryptophan, L-carnitine and adenosine diphosphate, changes in the concentration of these substances in blood plasma and urine gave the best results in the likelihood of adverse pneumonia. It is crucial that the above-mentioned metabolites play an essential role in both the immune response and CEM, indicating a deep pathogenic link between the immune system and bioenergy [7, 11, 12, 14]. The study of enzymes intracellular activity of energy metabolism holds a special place in the characterization of CEM. Specifically, there is a close relationship between changes in succinate dehydrogenase (SDH) activity, lactate dehydrogenase (LDH), malate dehydrogenase, alpha-glycero-phosphate dehydrogenase, and the CAP severity [2, 4, 5]. It is important to note that the methods of

CEM indicators assessment are characterized by high cost and complexity. In addition to that, modern bioethical principles require widespread implementation of noninvasive diagnostic approaches in medicine particularly in pediatrics.

Besides it should be noted that change in metabolism is essential for adolescent due to the influence of sex hormones, that cause special attention to these patients in the CEM disorders study [7].

The aim of the work is to study the CEM features and to develop approaches for the early diagnosis of bioenergetic disorders in conditions of community-acquired pneumonia in adolescents.

#### MATERIALS AND METHODS OF RESEARCH

We conducted a retrospective study, enrolling 41 children aged 14-18 with confirmed CAP, who were undergoing treatment in the pulmonology department of Odesa children's municipal hospital N 2. The study group had the following gender composition: boys – 23 (56.10%), and girls – 18 (43.90%). The enrollment was carried out in accordance to the inclusion/exclusion criteria. Inclusion criteria – radiologically confirmed pneumonia, CAP's nature. Exclusion criteria – concomitant chronic respiratory and heart diseases, immunodeficiency state. The control group, which included relatively healthy children was identical to the main group in age-sex structure and the total number of children namely 41 children, including boys – 21 (51.22%) and girls – 20 (48.78%).

The design of the study involved three steps. The first step – a detailed study of patient's life history, medical history, general clinical examination, measurement of  $SaO_2$ , determination of C-reactive protein (CRP) by a qualitative method, microbiological examination of sputum hematological indices calculation, namely neutrophil/lymphocyte ratio (NLR), leukocyte intoxication index (LII) of Kalf-Caliph [10]. Laboratory tests were performed when the child was admitted to the department (3-7 days from the disease onset).

The second stage of the work involved determining the CEM indices. We determined the intracellular LDH and SDH activity in peripheral blood lymphocytes. Enzyme activity was evaluated

according to the Lloyd et al. method (1982) [3]. The LDH/SDH ratio was used for integrated estimation of shifts in CEM [1].

At the final stage of the work, a mathematical model for the prediction of CEM was developed on the base of social and health characteristics of children with CAP. For that purpose data were processed by logistic regression [13]. Diagnostic accuracy of the mathematical model was assessed by the ROC analysis, curves (AUCs). Diagnostic specificity and diagnostic sensitivity of the mathematical model were also calculated.

In order to compare patient characteristics the type of distribution was determined and appropriate descriptive statistics methods were applied. We determined the arithmetic mean (M), the arithmetic mean error (m), standard deviation ( $\sigma$ ) and parametric Student test. A P value <0.05 was taken as the threshold for statistical significance. The statistical analyses were performed using GNU Project (2015) (GNU PSPP (Version 0.8.5) [Computer Software]. Free Software Foundation. Boston, MA).

The work was performed in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical principles for medical research involving human subjects". Parents and official guardians of all children involved in the

study gave written informed consent after they had been provided with full information about the purpose of the study, its methods and procedures.

## RESULTS AND DISCUSSION

The study group of children with CAP had the following characteristics. The relevant etiological factor of CAP was identified only in 23 patients  $56.10 \pm 7.75\%$  according to the results of bacteriological examination. Among those cases in which the etiological factor was established, the gram-positive flora was definitely dominant –  $73.91 \pm 9.36\%$  ( $p=0.008$ ). Thus, in  $60.87 \pm 10.41\%$  cases, the etiological factor of the disease was *Streptococcus pneumoniae*, *Staphylococcus pneumoniae* was determined in  $13.04 \pm 7.18\%$  cases. The gram-negative flora was represented by *Haemophilus influenza*, which was diagnosed in  $17.39 \pm 8.08\%$  of patients. In addition, in  $8.70 \pm 6.01\%$ , the atypical nature of CAP was ascertained, in particular, the presence of IgM to *Chlamydia pneumoniae* in the diagnostic titer (specific IgM >1:16) was determined.

Table 1 shows features of the medical and social history in the study group of adolescents with CAP. Table 2 describes the concomitant pathological conditions that require regular medical check-ups.

Table 1

### Social and health anamnesis of children with CAP (P±m)

Adverse factor	Percentage of patients (%) (n=41)
Premature birth	2.44±2.41
Low birth weight	4.88±3.32
Early formula feeding, the first 4 months of life	14.63±5.52
Crowded place (>7 persons per household)	2.44±2.41
Passive smoking	31.71±7.27
Recurrent pneumoniae (at least two episodes of pneumonia in one year or three episodes ever with intercritical radiographic clearing of densities)	4.88±3.32
Recurrent respiratory tract infections	9.76±4.63

As for the history of the present illness, the fever duration more than three days was in  $53.66 \pm 7.76\%$  of the surveyed, and the fever duration for at least three days at the time of hospitalization was registered in  $21.95 \pm 6.46\%$  ( $p=0.002$ ) cases, along with that in  $24.39 \pm 6.71\%$  of patients there was no fever at the pre-hospital stage ( $p=0.006$ ). Fever above  $39^\circ\text{C}$  was found only in  $12.20 \pm 5.11\%$  of adolescents. The majority of patients were admitted to the hospital from 4<sup>th</sup> to 7<sup>th</sup> of the disease –  $60.98 \pm 7.62\%$ , hospitalization on the 3<sup>rd</sup> day of the disease was recorded in  $12.20 \pm 5.11\%$  ( $p=0.0014$ ) of

patients, and after the 7<sup>th</sup> day – in  $26.83 \pm 6.92\%$  ( $p<0.0001$ ). Cough was recorded in the dominant number of the surveyed –  $82.93 \pm 5.88\%$  and in  $17.07 \pm 5.88\%$  of patients there was no such a complaint ( $p<0.0001$ ). Intoxication signs such as poor appetite and fatigue were observed in  $56.10 \pm 7.75\%$  of patients. Diagnostically significant decrease in the saturation level was documented in  $26.83 \pm 6.92\%$  of the surveyed children with CAP. Antibiotic therapy at the outpatient stage (within one week before CAP verification) was performed in  $39.02 \pm 7.62\%$  of patients with CAP.

Table 2

**Concomitant pathological conditions of children  
with community-acquired pneumonia ( $P \pm m$ )**

Concomitant pathological condition	Percentage of patients (%) (n=41)
Chronic gastroduodenitis	$7.32 \pm 4.07$
Functional gastrointestinal tract pathology (Functional disorder of the biliary tract, irritable bowel syndrome, functional dyspepsia)	$26.83 \pm 6.92$
Chronic rhinosinusitis	$14.63 \pm 4.52$
Chronic adenoiditis	$2.44 \pm 2.41$
Chronic tonsillitis	$12.20 \pm 5.11$
Allergic rhinitis	$7.32 \pm 4.07$
Atopic eczema	$4.88 \pm 3.36$
Obesity	$7.32 \pm 4.07$
Thyroid insufficiency	$4.88 \pm 3.36$
Anemia	$7.32 \pm 4.07$

Evaluation of the clinical and laboratory examination results showed that CAP in adolescents was with accompanied leukocytosis in  $43.90 \pm 7.75\%$  of cases, neutrophilosis in  $36.59 \pm 7.52\%$ , and an erythrocyte sedimentation rate (ESR) above  $20 \text{ mm/h}$  – in  $51.22 \pm 7.81\%$  of cases. The hematologic indices calculation determined the NLR increase in a significant number of patients, namely

– in  $70.73 \pm 7.11\%$  of cases ( $p=0.00018$ ), a LII increase by Kalf-Caliph was established in  $26.83 \pm 6.92\%$  of cases and an absolute number of lymphocyte decrease – in  $24.39 \pm 6.71\%$ . The increased C-reactive protein value was set in  $48.78 \pm 7.81\%$  of patients.

The morphological structure of CAP was characterized by the segmental type dominance, which

was determined in  $85.37 \pm 5.52\%$  of patients, focal type was diagnosed in  $14.63 \pm 5.52$  ( $p < 0.0001$ ). Local pleural complications, in particular encysted pleurisy were recorded in  $14.63 \pm 5.52\%$  of the surveyed.

The study of CEM parameters revealed inhibition of the SDH activity ( $2.01 \pm 0.085$ ) C.U. in patients with CAP relative to the parameters of control group ( $2.74 \pm 0.066$ ) C.U. ( $p < 0.001$ ), which indicated the presence of disorders in the Krebs cycle functioning. Along with that a significant increase in the average

LDH activity rate ( $3.92 \pm 0.060$ ) C.U. in children with CAP was not determined, compared with the average LDH activity rate in the control group – ( $4.11 \pm 0.081$ ) C.U. ( $p > 0.05$ ). It should be noted that there was an increase of the LDH/SDH index ( $2.11 \pm 0.082$ ) C.U. in adolescents with CAP, which indicated the inhibition of aerobic CEM processes and subsequent activation of anaerobic ones. The corresponding index in the control group was ( $1.42 \pm 0.037$ ) C.U. ( $p < 0.001$ ) (Table 3).

Table 3

Enzyme activity of the lymphocytes in children with CAP ( $M \pm m$ )

Measures Groups	Control group n=41	Children with CAP n=41	p - value
SDH, C.U.	$2.74 \pm 0.066$	$2.01 \pm 0.085$	$< 0.001$
LDH, C.U.	$4.11 \pm 0.081$	$3.92 \pm 0.060$	$> 0.05$
LDH/SDH ratio, C.U.	$1.42 \pm 0.037$	$2.11 \pm 0.082$	$< 0.001$

Rates of enzyme activity and indices calculated on their basis (Table 3) were subjected to further statistical processing by logistic regression. Thus, diagnostic mathematical models were constructed for detecting children with CAP with impaired CEM. It was possible to build models with sufficient accuracy only in those cases when the LDH activity and the LDH/SDH ratio were taken as a grouping attribute. The fact of CEM disorder was established in case of the CEM index excision the  $M \pm 2\sigma$  interval of the corresponding indicator in the control group.

At the final stage of the study, coefficients were set for each of the explanatory signs, using the logistic regression method. The next step was to establish the best combination of logistic regression coefficients to ensure the highest quality of the mathematical model and to reduce the number of explanatory signs included in the equation. The total number of explanatory signs was 37 quantitative and qualitative characteristics of CAP, which were listed above and presented in Tables 1 and 2.

For reliable differentiation of children with CAP with reduced SDH activity, and those with the decrease in SDH activity by more than  $2\sigma$ , relative to the control group –  $2.74 \pm 0.84$  C.U. ( $M \pm 2\sigma$ ), did not occur, the following logistic regression equation which contained 20 explanatory signs was built.

$$y = 0.003 + b_1 \cdot x_1 + \dots + b_{20} \cdot x_{20} \quad (1),$$

where,  $x_1$  – female gender (yes-1/no-0),  $b_1$  – (-0.438);  $x_2$  – passive smoking (yes-1/no-0),  $b_2$  – 0.27;  $x_3$  – chronic ENT pathology (yes-1/no-0),  $b_3$  – 1.024;  $x_4$  – atopic dermatitis (yes-1/no-0),  $b_4$  – (-0.584);  $x_5$  – chronic gastroenteritis (yes-1/no-0),  $b_5$  – 0.462;  $x_6$  – obesity (yes-1/no-0),  $b_6$  – 0.33;  $x_7$  – prematurity (yes-1/no-0),  $b_7$  – (-0.129);  $x_8$  – illness duration before hospitalization (number of days),  $b_8$  – 0.665;  $x_9$  – fever duration at the pre-hospital stage (number of days),  $b_9$  – 0.684;  $x_{10}$  – fever above  $39^\circ\text{C}$  (yes-1/no 0),  $b_{10}$  – 0.059;  $x_{11}$  – focal pneumonia (yes-1/no 0),  $b_{11}$  – 0.8;  $x_{12}$  – complicated pneumonia (yes-1/no 0),  $b_{12}$  – 0.15;  $x_{13}$  – absolute white blood cell count,  $b_{13}$  – 0.4;  $x_{14}$  – relative lymphocyte count,  $b_{14}$  – (-0.301);  $x_{15}$  – relative mature neutrophils count,  $b_{15}$  – (-0.005);  $x_{16}$  – relative band neutrophil count,  $b_{16}$  – 0.329;  $x_{17}$  – ESR,  $b_{17}$  – (-0.17);  $x_{18}$  – LII by Kalf-Caliph,  $b_{18}$  – (-0.899);  $x_{19}$  – NLR,  $b_{19}$  – (-0.094);  $x_{20}$  – absolute lymphocyte count,  $b_{20}$  – 0.164.

The ROC analysis was applied to the obtained model, which established the following model characteristics: AUC – 0.82, which indicated the "very good" work of the mathematical model, diagnostic specificity – 71%, diagnostic sensitivity – 90%.

The following logistic regression equation separates groups of patients with CAP with a normal LDH/SDH ratio and patients in whom this marker increased by more than  $2\sigma$ , relative to the control group, which was  $1.42 \pm 0.48$  C.U. ( $M \pm 2\sigma$ ). The mathematical model consisted of only 4 explanatory signs and corresponding coefficients:

$$y = -0.061 + b_1 \cdot x_1 + \dots + b_4 \cdot x_4 \quad (2),$$

where,  $x_1$  – relative lymphocyte count,  $b_1$  – (-0.117);  $x_2$  – relative mature neutrophils count,  $b_2$  – 0.048;  $x_3$  – relative band neutrophils count,  $b_3$  – 0.114;  $x_4$  – NLR,  $b_4$  – 0.036;

The area under the ROC curve was AUC – 0.78, which indicated the "good" mathematical model



quality. The following operating characteristics of the mathematical model were determined: diagnostic specificity – 69%, diagnostic sensitivity – 81%.

Analysis of this study results showed that there are significant changes in CEM in adolescents with CAP, which manifest themselves in significant SDH reduction – a key enzyme of the Krebs cycle and in the LDH/SDH index increase, indicating a CEM shift toward anaerobic (less efficient) energy synthesis. Similar results were obtained in studies performed by other researchers but they identified more profound changes in CEM due to age differences of the examined children (average age 6 years) [2]. Similar changes in CEM were recorded by a group of authors in a study that included adult patients with complicated pneumonia [5].

Modern medical science cannot be limited to only high-precision clinical-laboratory methods, but it also requires progressive statistics for processing of the obtained data. This approach aims to create an informative and accessible way to detect changes in various disorders in children. Each of the given above mathematical models has certain advantages and disadvantages. The advantage of the first one is its high sensitivity and specificity in determining CEM disorders and the disadvantage is the large number of patient's characteristics that need to be evaluated. Regarding the second formula, it exhibits poorer sensitivity and specificity than the first formula but is relatively simple to calculate and includes only clinical blood counts and hematologic indices. The implementation of this study results significantly expands the diagnostic possibilities for the assessment of CEM and will allow separating the most vulnerable category of patients in order to prevent further chronization of acute inflammatory

diseases, taking into account the individual characteristics of the organism.

Consequently, the focus of our study on the development of approaches for the noninvasive, accessible and cost-effective detection of changes in CEM in children with CAP is a feature of our work distinctive from other studies in this area.

Prospects for future research we see in the expansion of clinical groups for which this approach should be applied and in the methods development for the patients' differentiation according to the depth of CEM lesions in children with CAP, in order to identify the most vulnerable patients who should undergo a more detailed examination of their CEM, appropriate correction, and in some cases – counseling at the medical-genetic center.

## CONCLUSIONS

1. In children with CAP aged 14-18 years changes in CEM, such as decreased SDH activity and elevation of the LDH /SDH ratio were found.

2. The comprehensive assessment of informativeness of clinical and anamnestic indicators and the cell-energy metabolism analysis results in CAP in adolescents was proved, this was confirmed by statistical methods and the effectiveness of the proposed mathematical models having significant diagnostic value. The developed models allow predicting the presence of changes in cellular energy metabolism, namely a decrease in LDH activity (AUC=0.82; Sp=71%; Se=90%) and an increase in the LDH/SDH index (AUC =0.78; Sp=69%; Se=81%) in the first days after the diagnosis of community-acquired pneumonia.

Conflict of interests. The authors declare no conflict of interest.

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