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PREDICTIVE ROLE OF BACTERICIDAL/PERMEABILITY-INCREASING PROTEIN AND C-REACTIVE PROTEIN IN A PERSONALIZED APPROACH TO THE TREATMENT OF CHILDREN WITH ACUTE PNEUMONIA

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ПРОГНОСТИЧЕСКАЯ РОЛЬ АНТИМИКРОБНОГО БЕЛКА, ПОВЫШАЮЩЕГО ПРОНИЦАЕМОСТЬ КЛЕТОК, И С-РЕАКТИВНОГО БЕЛКА ПРИ ПЕРСОНАЛИЗИРОВАННОМ ПОДХОДЕ К ЛЕЧЕНИЮ ДЕТЕЙ С ОСТРЫМИ ПНЕВМОНИЯМИ

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Our prospective nonrandomized controlled study enrolled 165 children with acute pneumonia (AP) from 2 to 18 years of age, which included 51 (30.9 %) children with ANP. There were 91 (55.2 %) boys and 73 (44.8 %) girls. Dynamic complex determination of BPI and CRP concentrations in blood serum from children with AP was a sensitive indicator to predict the development of complications and ANP. High levels of BPI and CRP in children with AP were prognostic signs for good outcomes of the disease. In the presence of an initially low BPI level (<10 ng/ml) and high CRP (>100 mg/L), disease progression was noted, which included the development of bronchopleural complications.

Keywords: acute pneumonia, BPI, CRP, necrotizing pneumonia, inflammation, children

В проспективное нерандомизированное контролируемое исследование были включены 165 детей от 2 до 18 лет с острой пневмонией, в том числе 51 (30,9 %) ребенок с острой гнойно-деструктивной пневмонией (ОГДП). Мальчиков было 91 (55,2 %), девочек – 73 (44,8 %). Динамическое комплексное определение концентрации антимикробного белка, повышающего проницаемость клеток (BPI), и СРБ в сыворотке крови у детей с острой пневмонией является чувствительным показателем в прогнозировании развития осложнений и ОГДП. Высокий уровень BPI и СРБ у детей с острой пневмонией является благоприятным прогностическим признаком в отношении исхода заболевания. При наличии исходно низкого уровня BPI (менее 10 нг/мл) и высокого уровня СРБ (более 100 мг/л) отмечается неблагоприятное течение заболевания, включая и развитие бронхоплевральных осложнений.

Ключевые слова: острая пневмония, антимикробный белок, повышающий проницаемость клеток, СРБ, ОГДП, воспаление, дети

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AD – antibacterial drug
ANP – acute necrotizing pneumonia
AT – antibiotic therapy
BPI – bactericidal permeability-increasing protein
EBV – Epstein-Barr virus
ELISA – enzyme-linked immunosorbent assay
CMV – cytomegalovirus
CRP – C-reactive protein
PCR – polymerase chain reaction

Predicting the course of the inflammatory reaction and the development of complications in children with acute pneumonia (AP) has been difficult [1–5]. The result of the inflammatory process is associated with impaired permeability of cell membranes and subsequent translocation of microflora through the alveolar epithelium and basement membrane [6–9].

Interest in proteins of the acute phase of inflammation (e.g., CRP, serum amyloid P, and mannose-binding lectins) remains invariably high. Studies of endogenous antimicrobial peptides are gaining increasing attention, particularly bactericidal/permeability-increasing protein (BPI) [10–12]. BPI is a neutrophilic derived protein and the prototype of the tubular lipid-binding protein family. A study has described the location and effectiveness of BPI in gram-negative and -positive bacteremia and sepsis [13]. Additionally, the serum BPI concentration increases not only during inflammatory diseases, but also during allergic reactions [14]. Because of the limited number of studies devoted to comprehensive assessment of BPI and CRP levels during the progression of AP and acute necrotizing pneumonia (ANP) in children, this research area is relevant and in demand.

This study aimed to comprehensively assess the effect of BPI and CRP levels on the development of AP in children.

Material and Methods. The prospective non-randomized controlled study included 165 children aged 2–18 years with a respiratory tract infection accompanied by development of pneumonia, which included 51 (30.9 %) children with ANP. There were 91 boys (55.2 %) and 73 girls (44.8 %).

This study was carried out by following the requirements of biomedical ethics of the Geneva Convention on Human Rights (1997) and the Declaration of Helsinki of the World Medical Association (2000) and received permission from the local ethics committee, which included informed consent from parents and patients for inclusion in the study.

Analysis of children with AP revealed a predominance of patients of preschool age (3–6 years) [64 (38.8 %) children], which included 37 boys (22.4 %) and 27 girls (16.9 %). The distribution of patients by age and sex is shown in the Figure.

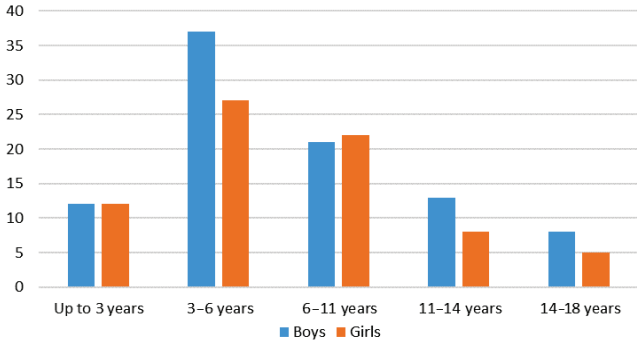

Fig. Distribution of patients with AP by age and sex

Patients with AP were admitted to hospital on average at 10.3±0.6 days from the onset of disease. Early diagnosis and hospitalization at 3–7 days from the beginning of the disease had occurred for 58 (35.2 %) children. Additionally, admission to the hospital for more than half of the cases [107 (64.8 %)] was late (later than 8 days from the onset of the disease).

The criteria for inclusion of patients in the study were as follows. Age of patients: 2–18 years; X-ray-confirmed diagnosis of pneumonia; absence of severe concomitant pathology; absence of allergic reactions to administration of drugs; signing voluntary consent for participation in this study by patients and their parents.

Exclusion criteria for patients were as follows. Age of patients: under 2 or over 18 years; absence of a radiographically confirmed diagnosis of AP; previous hospitalization of the patient in a hospital that required the use of ABT within a period of up to 30 days; nosocomial pneumonia; concomitant somatic and infectious diseases; the use of glucocorticoids; refusal of patients and their parents to participate in this study.

Children were divided into three groups: group 1 included 82 (49.7 %) patients with AP; group 2 included 32 (19.4 %) children who had progression or lack of dynamics in the treatment of AP in the course of treatment; group 3 included 51 (30.9 %) patients with ANP. The control group consisted of 25 healthy children admitted to somatic and surgical departments for non-infectious diseases (e.g., inguinal hernia and intestinal colic).

Children underwent clinical and instrumental examinations that included laboratory techniques that followed generally accepted standards (e.g., general blood and urine analyses, biochemical blood tests, including total protein and its fractions, total bilirubin and fractions, transaminases, urea, and creatinine). Upon admission, all patients underwent microbiological analyses that included smear prints from the mucous membrane of the upper respiratory tract for microflora and sensitivity to ABT as well as PCR testing for respiratory viruses. During the course of treatment, all children underwent an ELISA of blood plasma to detect chlamydia, toxoplasma, mycoplasma, Epstein-Barr virus, CMV, and herpes simplex virus types I and II.

Along with laboratory examinations, patients underwent ultrasound of the pleural cavity and pulmonary parenchyma and X-ray examination (plain radiography and CT).

Dynamic monitoring of CRP in children with AP was carried out at the bedside using a portable immunochromatographic express analyzer Easy-Reader (VedaLab, Alençon, France). In blood sera of children with AP, BPI was measured by an ELISA in an automatic analyzer using a standard set of reagents. For this analysis, we used reagents from BCM Diagnostics (Elston Way, Woodland, USA). Blood analyses for the levels of CRP and BPI in blood plasma from children were carried out upon admission and on the third and 14th days after the patient was admitted to hospital.

Patients received complex etiotropic, pathogenetic, and symptomatic therapies for the underlying disease and concomitant pathology.

Analysis of the differences among groups was carried out by variation statistics using Microsoft Excel 2010 (Microsoft Office, USA) and Statistica 10.0 (StatInc, USA). The normality of the distribution of variation series was checked using Kolmogorov and Shapiro–Vilks goodness-of-fit tests. Correlation analysis in accordance with Mann–Whitney was carried out by calculation of the U-empirical criterion and determination of the zone in which the results were located (significance, uncertainty, and insignificance).

Results and Discussion. All children with AP showed a significant increase in the concentration of antimicrobial proteins that increased the permeability of BPI cells compared with healthy children ($p<0.01$) (Table 1). This unambiguously revealed a pronounced anti-inflammatory response in children with pneumonia.

The changes in the concentration of bactericidal protein BPI among patients showed that its baseline level had increased in all groups throughout the study, which reached a maximum by 14 days.

Table 1

BPI concentration (M±m) in blood serum of children in the study groups (ng/ml)

Research timing	Comparison group n=25	Group 1 n=82	Group 2 n=32	Group 3 n=51
Upon hospital admission	2.2±0.5	15.8±3.1	17.3±2.2	9.5±1.8**
On the third day of inpatient treatment		21.7±2.5	17.9±2.6	16.2±3.3
On day 14 of inpatient treatment		24.4±3.6	23.1±2.8	33.6±4.5#

** – in comparison, groups 2 and 3 – $p<0.01$.
# – within the group in comparison upon admission and on day 14 – $p<0.01$.

Moreover, each group had its own level of increase in the studied parameters. Therefore, group 1 had a progressive increase in the BPI concentration from admission to the period of convalescence (15.8±3.1 and 24.4±3.6 ng/ml, respectively). In group 2, there was a feature associated with «stagnation» of the BPI level at 17.9±2.6 ng/ml in comparison with its increase in group 1 (21.7±2.5 ng/ml). This indicated the need to revise the treatment program, which included correction of ABT. The correction led to a good treatment result and equalization of the BPI concentration during the recovery period in both groups.

In group 3 children with ANP, the concentration of BPI was much lower than in children with AP, which was 9.5±1.8 ng/ml. Against the background of adequately conducted treatment, a significant increase to 33.6±4.5 ng/ml was noted by the 14th day ($p<0.05$).

The serum level of CRP in children was significantly decreased from admission to 14 days of hospitalization ($p<0.01$) and was significantly high in all children at the time of hospitalization in comparison with healthy respondents ($p<0.01$) (Table 2). The dynamics of CRP demonstrated the adequacy of the therapeutic measures in patients with pneumonia.

Similar to the changes associated with BPI, the individual characteristics of the change in concentration were recorded for each group. In groups 1 and 2, there was a progressive decrease in the level of CRP in blood plasma from admission to the period of recovery (98.7±15.1 and 2.2±0.6 mg/L; 112.4±27.9 and 2.9±0.4 mg/L, respectively). In group 2, there was a higher CRP level than in group 1. A high baseline BOP rate required closer attention from the attending physician. The changes in the CRP level among patients with ANP showed the highest rates among all participants upon admission to the hospital (136.5±8.7 mg/L).

Table 2

Serum CRP level (M±m) in children in the study groups (mg/L)

Research timing	Comparison group n=25	Group 1 n=82	Group 2 n=32	Group 3 n=51
Upon hospital admission	2.1±0.3	98.7±15.1	112.4±27.9	136.5±18.7
On the third day of inpatient treatment		44.1±5.9	56.4±7.5	70.6±9.3&
On day 14 of inpatient treatment		2.2±0.6#	2.9±0.4#	4.9±1.2#, &

& – in comparison, groups 1 and 3 – $p<0.05$.
# – within the group in comparison upon admission and on day 14 – $p<0.01$.

On the basis of the results of dynamic determination of BPI and CRP concentrations, we analyzed the dynamics and trends of their changes, which allowed us to not only to predict the development of a complicated course of AP in children, but also correct the treatment.

With a complicated course of AP in children and initially high serum concentrations of BPI and CRP in patients from the onset of illness, by the third day of inpatient treatment, stagnation of the BPI concentration was noted. However, a decrease in CRP was observed, but it did not reach the range of values of the uncomplicated course of AP. This combination of serum BPI and CRP suggested a change in the treatment approach, which included correction of the antibiotic therapy. Modification of the treatment program provided a favorably high concentration of BPI with a low serum CRP level by the 14th day.

Endogenous antimicrobial peptides and proteins are essential components of the innate immune system that protects against various bacteria, fungi, and viruses [15]. BPI is abundant in primary azurophilic granules and is associated with the airway epithelial cell surface [16, 17]. During AP, BPI is central to antimicrobial protection. During phagocytic uptake of bacteria by neutrophφils, primary granules rapidly degranulate in the phagosome, which leads to direct destruction of pathogens by very high local concentrations of BPI and other antimicrobial peptides [18].

In children with early clinical manifestations of sepsis, the BPI level increases significantly and is comparable to that in adults with bacteremia or pneumonia. In this regard, it is very promising to determine BPI in plasma as a marker of systemic inflammation and bacterial infection. Additionally, BPI is an endogenous inhibitor of angiogenesis by inducing apoptosis of vascular endothelial cells [19, 20].

BPI is a marker for various diseases. Autoantibodies against BPI are a serological marker of inflammatory diseases such as cystic fibrosis of the pancreas, vasculitis, and primary sclerosing cholangitis. BPI concentrations in plasma and synovial fluid of patients with rheumatoid arthritis correlate with disease activity [21–23].

Determination of only BPI in AP does not always lead to a positive and unambiguous interpretation of the study result. Thus, the authors did not detect an increase in anti-BPI IgA in saliva. However, the mucous surface is where bacteria with neutrophils are present, which accumulate

during the infectious process [24, 25]. However, saliva may have an unusual BPI concentration [21].

Our study found that a comprehensive dynamic survey of the concentrations of BPI and CRP in blood sera of children with AP is a sensitive indicator to predict the development of complications and ANP.

Conclusions. A high BPI level with an accompanying high serum CRP level in children with a respiratory tract infection upon admission to a hospital is a favorable prognostic sign for the outcome of the disease. An initially low BPI level in blood serum (<10 ng/ml) in children with a high level of CRP (>100 mg/L) is a marker of an unfavorable course of the disease and the development of pulmonary-pleural complications. Determination of the dynamics of BPI and CRP concentrations in children with AP may serve as an early predictor for changes in treatment tactics.

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IMMUNOGENETIC FEATURES OF DIFFERENT FORMS OF SECONDARY PYELONEPHRITIS IN CHILDREN

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ИММУНОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ РАЗЛИЧНЫХ ФОРМ ВТОРИЧНОГО ПИЕЛОНЕФРИТА У ДЕТЕЙ

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In recent years, many studies have documented an increased incidence of urinary system pathology in children, especially congenital anomalies of the urinary system with secondary pyelonephritis (SP). We carried out immunogenetic typing in 200 children aged 5–15 years with SP (100 children with latent SP and 100 children with recurrent SP). The distribution of human leukocyte antigen (HLA) alleles at the A, B, C, DR, DQ loci, as well as their phenotypic and haplotype combinations, was determined. We found that the latent course of SP in children was associated with interlocus combinations of the class 1 antigens HLA-A2/B17 and HLA-A3/B13. Resistance to latent SP was associated with the alleles HLA-DRB1*07, HLA-DRB1*15 (2), and HLA-DQB1*0302, the phenotypic combinations of antigens HLA-A1/A9 and HLA-A9/A11, and the haplotype combinations HLA-A3/B7, HLA-A11/B35, and HLA-A19/B27. The recurrent course of SP in children was associated with the haplotype combination HLA-A11/B27. Resistance to recurrent SP was associated with the alleles HLA-DRB1*07, HLA-DRB1*09, and HLA-DRB1*15 (2), the intralocus antigenic combination HLA-A9/A11, and the interlocus combinations HLA-A2/B12, HLA-A3/B7, and HLA-A11/B35. In conclusions, HLA typing in children with various forms of SP enables the identification of factors predisposing to the development of this disease. These data may help clinicians understand the prognosis and disease course of various forms of SP.

Keywords: secondary pyelonephritis, immunogenetics, HLA, children