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ANALYSIS OF THE RISK OF RECURRENT WHEEZING IN CHILDREN WITH BRONCHIOLITIS BASED ON THE WEIBULL MATHEMATICAL MODEL

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Introduction

Given the frequency of recurrent wheezing (up to 50 % of cases) in young children during the first year after bronchiolitis, the assessment of the prognostic value of diagnostic biological markers of bronchiolitis requires special attention.

According to modern concepts, mast cells, eosinophils, play a significant role in the pathogenesis of bronchiolitis, with degranulation of which the release of cationic proteins (eosinophilic cationic protein (ECP), eosinophil-derived neurotoxin (EDN)) and molecular mediators, namely vascular cell adhesion molecule-1 (VCAM-1), which is a regulator of leukocyte adhesion and transendothelial migration. That is why VCAM-1, ECP and EDN are discussed as important prognostic markers in assessing the risk of recurrent wheezing in children with bronchiolitis.

The aim of the study. *To analyze the risk factors for recurrent wheezing in children with bronchiolitis, considering allergic history, the influence of external factors (passive smoking, place of residence), levels of VCAM-1, ECP, EDN in the blood serum.*

Material and Methods. *This article is a part of the research work of the Department of Paediatrics No. 1 of Vinnytsia National Medical University named after M.I. Pyrohov on the topic "Optimization of diagnosis and treatment of somatic pathology in children", state registration No. 0115U007075.*

A clinical examination of 67 infants was carried out. The main group consisted of 34 children with bronchiolitis without a complicated allergic history. The comparison group consisted of 33 children with bronchiolitis who had a burdened allergic history. The average age of the children in the main group was 8.4±1.6 months, and 6.2±1.4 months in the comparison group. The analytical component of the study was based on parametric survival models (Weibull and generalized Gamma models). The analysis of Weibull models was performed in the statistical packages of analytical system R for Mac OS X FAQ, Version 3.1.0 2014-04-10, R. app 1.64 based on the Mac OS X 10.9 platform, 64-bit Intel Core i7 architecture.

The study was approved by the Commission on Biomedical Ethics for compliance with the moral and legal rules for conducting medical research at Vinnytsia National Medical University named after M.I. Pyrohov. It was established that the research does not contradict the basic bioethical norms and meets the principles of compliance with the basic provisions of the GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2008) and Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009 (as amended by Order of the Ministry of Health of Ukraine No. 523 of 12.07.2012). All patients were informed about the purpose and possible consequences of the research procedures. All patients signed an informed written consent to participate in the study prior to the procedure.

Results of the study. *The risks of recurrent wheezing in children with bronchiolitis according to the Weibull model were allergic history (β=1,996) mixed feeding, and to an even greater extent artificial feeding (β=7,832 and β=8,337). High serum levels of ECP β=5,03, EDN β=0,182 and VCAM-1 β=0,0254 are reliable markers of increased risk of recurrent wheezing in children with bronchiolitis. Living in rural areas (β=-5,8) significantly reduces the risk of recurrent wheezing in children with bronchiolitis compared to children living in urban areas β=0.0162).*

Conclusions*. 1. The levels of VCAM-1, ECP and EDN in the blood serum were recognized as reliable markers for the prognosis of recurrent vesicitis in children with bronchiolitis. The level of EDN ≤ 7 ng/ml in the blood serum is a prognostic marker for the risk of recurrent wheezing in children with bronchiolitis.*

2. The hypothesis that artificial feeding in children with bronchiolitis with a complicated allergic history confirms and significantly increases the risk of recurrent vesicitis in children with bronchiolitis. The hypothesis about the role of passive smoking exposure in a significant increase in the risk of recurrent wheezing in children with bronchiolitis was confirmed only for patients with EDN levels not exceeding 7 ng/ml in the blood serum.

Key words: *Bronchiolitis; Recurrent Wheezing; Bronchial Obstruction; Children; Early Age; Mathematical Model; Vascular Cell Adhesion Molecule-1; Eosinophilic Cationic Protein; Eosinophil-derived Neurotoxin.*

Introduction

Modern research is increasingly focusing on the course of bronchiolitis in young children, as this disease remains the leading cause of not only hospitalization but also recurrent wheezing [1, 3]. Today, the study of the cause-and-effect relationships of pathophysiological changes in the bronchial tree in bronchiolitis remains relevant [2].

According to current concepts, mast cells, eosinophils, play a significant role in the pathogenesis of bronchiolitis, with their degranulation releasing inflammatory mediators (histamine, cationic proteins, cytokines, leukotrienes) and molecular mediators, namely vascular cell adhesion molecule-1, which is a

regulator of leukocyte adhesion and transendothelial migration. Exposure to an infectious factor in bronchiolitis increases the expression of this molecule on the respiratory endothelium by supporting leukocyte infiltration [4].

Studies have confirmed that the genesis of bronchiolitis is closely related to hereditary predisposition to atopy and allergic history [5]. In allergic inflammation, eosinophils enhance the inflammatory response of the airways, which leads to bronchiolar edema, mucus hyperproduction, and subsequent remodeling of the respiratory epithelium [6]. Eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) are the main proteins contained in eosinophil granules and are markers of eosinophil-mediated inflammation in bronchial tree lesions [7, 8]. For this reason, serum levels of VCAM-1, ECP and EDN are suggested as markers of bronchiolitis severity [9, 10]. However, the issue of their prognostic value in the risk of recurrent wheezing in children with bronchiolitis remains unresolved.

The aim and objectives of the study

To analyze the risk factors for recurrent wheezing in children with bronchiolitis, considering history, the influence of external factors (passive smoking, place of residence), levels of VCAM-1, ECP, EDN in the blood serum.

Material and Methods

This article is a part of the research work of the Department of Paediatrics No. 1 of Vinnytsia National Medical University named after M.I. Pyrohov on the topic "Optimization of diagnosis and treatment of somatic pathology in children", state registration No. 0115U007075.

A clinical examination of 67 young children was carried out. The main group consisted of 34 children with bronchiolitis without a complicated allergic history. The comparison group consisted of 33 children with bronchiolitis who had a complicated allergic history. The average age of the children in the main group was 8.4±1.6 months, and in the comparison group - 6.2±1.4 months. The inclusion criteria for the study were: children with bronchiolitis, full-term infants, children aged 0 to 12 months, informed consent from the child's parents to participate in the study. The exclusion criteria were children with congenital malformations of the bronchopulmonary system or cardiovascular system, children with bronchopulmonary dysplasia, gastroesophageal reflux disease and preterm infants.

The analytical component of the study was based on parametric survival models (Weibull and generalized Gamma) [11-13]. Weibull models were analyzed in the packages of the statistical analytical system R for Mac OS X FAQ, Version 3.1.0 2014-04-10, R. app 1.64 based on the Mac OS X 10.9 platform, 64-bit Intel Core i7 architecture [14-16].

The model parameters were calculated in a package using the Gibbs sampler and the Hamiltonian dynamics (Hamiltonian Dynamic Sampler) [17,18]. The dependent variable of the model was the time to the first signs of recurrent wheezing after inpatient treatment for bronchiolitis. Predictors included were the child's age, place of residence, history of allergic manifestations, passive smoking, type of feeding, serum levels of VCAM-1, ESR and EDN, and severity of bronchiolitis (assessed through the proxy variable "duration of hospitalization"). Preliminary data preparation and convergence studies in Markov chains were performed using the mathematical analytical system R version 3.1.0 based on the CODA package. All the graphical images presented here were also created in R (GRAPHICS package) [14].

The study was approved by the Commission on Biomedical Ethics for compliance with the moral and legal rules for conducting medical research at Vinnytsia National Medical University named after M.I. Pyrohov. It was established that the research does not contradict the basic bioethical norms and meets the principles of compliance with the basic provisions of the GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2008) and Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009 (as amended by Order of the Ministry of Health of Ukraine No. 523 of 12.07.2012). All patients were informed about the purpose and possible consequences of the research procedures. All patients signed an informed written consent to participate in the study prior to the procedure.

Research results and discussion

The analysis of the heterogeneity of EDN levels in the blood serum revealed two groups of children differ by its value. For a detailed study of serum EDN levels as a risk factor for recurrent wheezing, we analyzed its distribution among the groups of children examined (Fig. 1-2).

Clearly, a serum EDN level of 7 ng/ml is the threshold for the allocation of group 1 of 28 children with an EDN $\leq$ 7 ng/ml. For children in group 1, we applied f model with separate linear predictor and scaling parameter, yet integrated by a single likelihood function, which greatly increases the reliability of the estimator.

To assess the quality of the description of the two-population model data, we created histograms for the distribution of two types (Martingale and Deviance) of residuals (Figs. 3-4). These distributions are indicative of the reproduction of the patterns obtained in a heterogeneous population of patients. Thus, in the pathogenetic mechanisms of allergic inflammation, the basis of heterogeneity was the level of EDN in the blood serum. An increase in this marker may indicate the degree of activation of the main pro-inflammatory cells of allergic inflammation, and thus indirectly the severity of the inflammatory process with bronchiolitis.

Hypothesis testing was based on regression effect estimates using two models. The single-population Weibull model provides less valid estimates because not all included predictors of risk.

The results of the single-population Weibull model are shown in Table 1. The Parameter column describes the name of the model parameter from the software script. The Effect column indicates the effect that the parameter estimates. Parameter estimates can be found in the Estimate column. The standard errors of the parameter estimates are listed in the "m" column, as this letter denotes sampling error.

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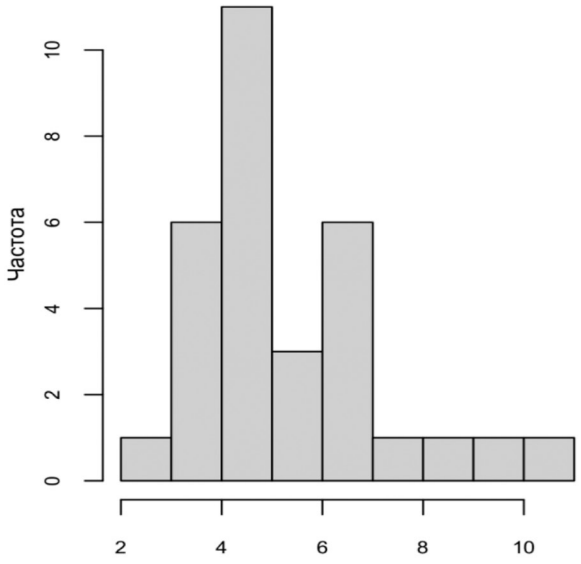

Fig. 1. Distribution of EDN values in the first group

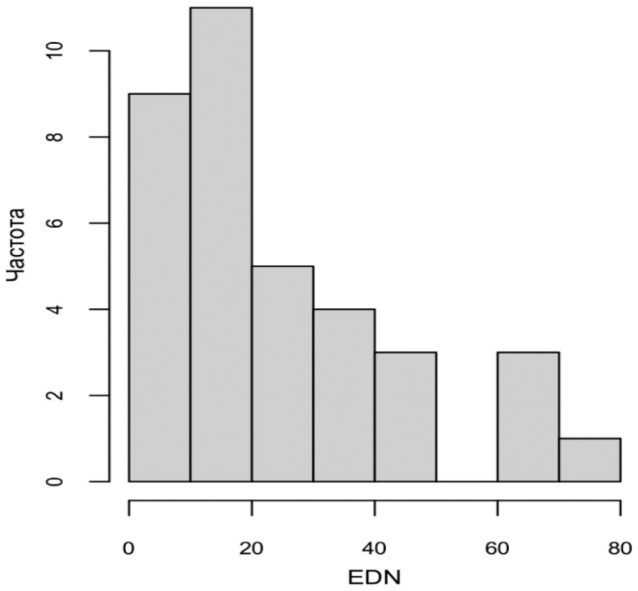

Fig. 2. Distribution of EDN values in the second group

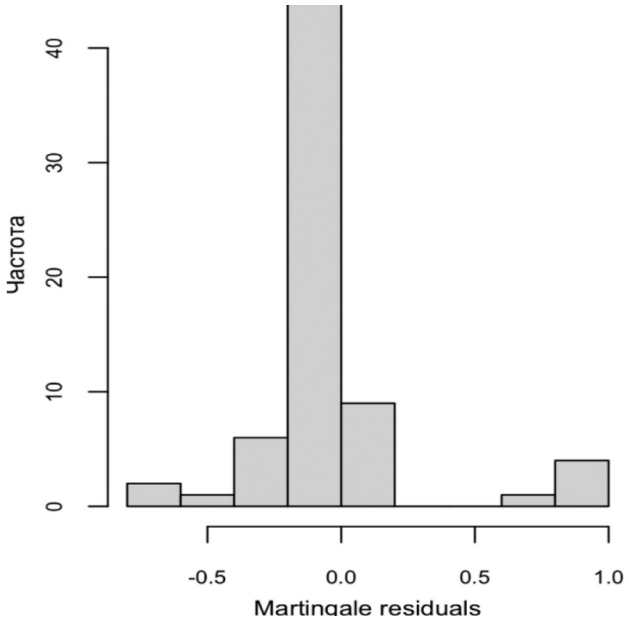

Fig. 3. Distribution of Martingale residuals of the two-population model

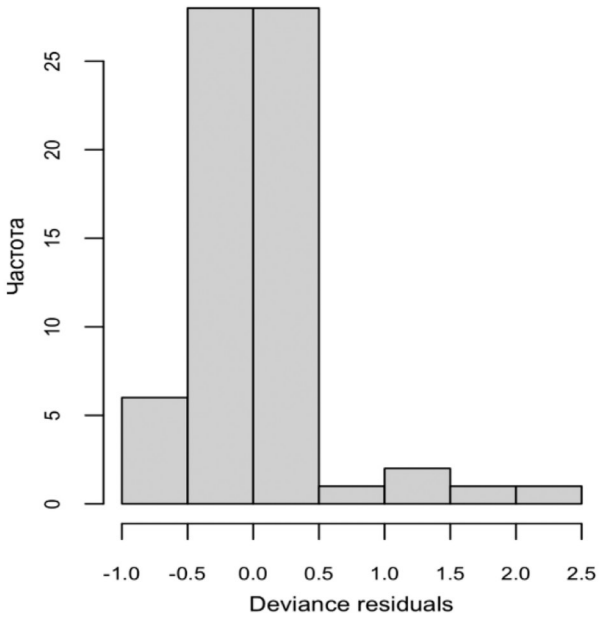

Fig. 4. Distribution of deviant residuals two-population model

The 95% confidence interval of the parameter estimate is represented by the 2.5% and 97.5% centiles of the posterior distribution of the MSMS sampling estimates. The regression effects are reliable if their confidence intervals do not contain zero values. According to the Weibull model, regression effects express the influence of a factor on the risk of recurrent wheezing. For example, the child's age has no significant effect on the risk of recurrent wheezing, as the 95% confidence interval includes zero: [-1,929; 1,170]. Negative values suggest a decreased risk of recurrent wheezing, whereas positive values indicate the opposite.

Thus, the reliable influence on the risk of recurrent wheezing in children with bronchiolitis was exerted according to the Weibull model by the following factors: residence in rural areas, RR=exp(1.017)=2.76; allergic history, RR=exp(0.691)=2.0; serum level of VCAM-1, RR=exp(1.097)=3.0; severity of bronchiolitis, RR=exp(1.433)=4.2.

The assessment of the booster effect of VCAM-1 on the modification of risk caused by EDN, as well as the effect of EDN itself, cannot be achieved within the framework of a single-population Weibull model, as mentioned earlier due to the presence of EDN heterogeneous populations among children with bronchiolitis. Therefore, it is more appropriate to test hypotheses regarding regression effects using a two-population model that incorporates heterogeneity through a composite likelihood function.

Importantly, the shape parameter kappa=6.624 indicates a small delay in the onset of recurrent wheezing, reducing the positive time dependence, that is, it poorly reproduces the delayed right-tailed cases of the time interval distribution before the onset of initial wheezing symptoms.

The results of the two-population

Weibull model are presented in Tables 2-3 in the context of the two populations. It is important

to understand that the parameters for both populations were estimated together through a composite likelihood function, and the respective parameter estimates are presented separately solely for the comprehensibility of examining the two heterogeneous populations of children. Thus, Table 2 shows the results of the two-population Weibull model for assessing the risk of recurrent wheezing in children with a history of bronchiolitis for the population of children (39 people) with high EDN levels (> 7 ng/ml) in the blood serum. The regression coefficients in the table and in the text of the software module are denoted as beta.

Thus, for children with bronchiolitis and high EDN levels in the blood serum, the following factors significantly influenced the risk of recurrent wheezing: residing in rural areas (β=-5.8) decreases the risk of recurrent wheezing; allergic history (β=1.996); mixed feeding, and to an even greater extent, artificial feeding (β=7.832 and β=8.337); deficiency and insufficiency of vitamin D (β=2.81); high level of IgE in serum (β=5.03); level of EDN in serum (β=0.182); level of VCAM-1 in serum (β=0.0254) are significant markers of increased risk of recurrent wheezing in children with bronchiolitis.

The duration of hospital stay for children with bronchiolitis (β=-1.82) is also a significant risk factor for recurrent wheezing.

Table 1

Results of the single-population Weibull model for assessing the risk of recurrent wheezing in children with bronchiolitis (according to anamnesis)

Effect.	Parameter.	Assessment.	m	2,5%	97,5%
Constant	beta[1]	0,7786	0,6739	0,1048	1,4525
Age of the child	beta[2]	-0,3794	1,5493	-1,9288	1,1699
Accommodation (village)	beta[3]	1,0167	0,7569	0,2598	1,7735
Allergic history	beta[4]	0,6910	0,0143	0,6767	0,7053
Passive smoking	beta[5]	-0,0471	1,3386	-1,3857	1,2915
Mixed feeding	beta[6]	-0,0231	1,1674	-1,1905	1,1444
Artificial feeding	beta[7]	-0,0612	1,0305	-1,0918	0,9693
Vitamin D concentration	beta[8]	-0,1463	0,3724	-0,5186	0,2261
ECP concentration	beta[9]	0,5441	1,2135	-0,6694	1,7576
IgE concentration	beta[10]	-0,4133	1,5431	-1,9564	1,1298
CC16 concentration	beta[11]	-0,1080	0,1576	-0,2655	0,0496
EDN concentration	beta[12]	-0,4033	1,5884	-1,9918	1,1851
VCAM-1 concentration	beta[13]	1,0969	0,0872	1,0097	1,1841
Severity of bronchiolitis	beta[14]	1,4333	0,3052	1,1281	1,7386
VCAM_ECP	beta[15]	-0,2683	0,4136	-0,6819	0,1454
VCAM_EDN	beta[16]	-0,3206	0,1437	-0,4644	-0,1769
Form	kappa	6,6242	0,6829	5,9414	7,3071
Std. deviation	sigma	0,1526	0,0157	0,1369	0,1683

Table 2

The results of the two-population Weibull model estimation of the risk of recurrent wheezing in children with bronchiolitis, (EDN > 7 ng/ml)

Effect.	Parameter.	Assessment.	m	2,5%	97,5%
Constant	beta[1]	-7,8454	0,2600	-18,6162	3,0831
Age of the child	beta[2]	-0,3773	0,0135	-0,9877	0,1423
Accommodation (village)	beta[3]	-5,8238	0,1131	-10,7472	-2,2757
Allergy history	beta[4]	1,9961	0,1505	0,1794	3,5399
Passive smoking	beta[5]	-1,3657	0,0977	-5,0526	2,0796
Mixed feeding	beta[6]	7,8317	0,0989	3,9828	12,4698
Artificial feeding	beta[7]	8,3371	0,1093	4,3640	13,5118
Vitamin D concentration	beta[8]	2,8105	0,0444	1,1899	4,8500
ECP concentration	beta[9]	-8,6840	0,3830	-23,7479	4,9894
IgE concentration	beta[10]	5,0301	0,1079	1,0511	10,4180
CC16 concentration	beta[11]	-0,1577	0,0030	-0,2768	0,0609
EDN concentration	beta[12]	0,1815	0,0045	0,0323	0,3763
VCAM-1 concentration	beta[13]	0,0254	0,0010	0,0117	0,0674
Severity of bronchiolitis	beta[14]	-1,8245	0,0385	-3,5799	-0,4877
VCAM_ECP	beta[15]	0,0490	0,0016	-0,0228	0,1284
VCAM_EDN	beta[16]	-0,0023	0,0000	-0,0043	0,0007
Form	kappa1	4,3067	0,0553	2,5291	6,5371

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Table 3 describes children with bronchiolitis with a very low risk of recurrent wheezing (the number of such children in the sample is 28). Thus, the constant of such children (b[1]= -2405) is significantly lower than the constant of the first population (beta[1]=-7.85). Additionally, the shape parameter for the second population of children (kappa2=159.2) significantly exceeds that of the first population of bronchiolitis patients (kappa1=4.31). These parameters indicate a significant delay in the occurrence of recurrent wheezing in the second population of children compared to the first. The second population of "resistant" children is located in the right tail of the distribution and includes half (20 out of 44) of the right-censored cases.

Table 3

Results of the two-population Weibull model for assessing the risk of recurrent wheezing in children with bronchiolitis (EDN ≤ 7 ng/ml)

Effect.	Parameter.	Assessment.	m	2,5%	97,5%
Constant	b[1]	-2405,45	214,62	-3112,50	-654,70
Age of the child	b[2]	-6,6086	3,2309	-21,6570	6,5431
Accommodation (village)	b[3]	517,80	73,73	145,27	779,95
Allergic anamnesis	b[4]	679,57	75,68	195,76	931,69
Passive smoking	b[5]	1114,77	113,17	323,92	1517,89
Mixed feeding	b[6]	-2483,62	1868,63	-7496,91	243,37
Artificial feeding	b[7]	767,33	71,20	218,44	1001,42
Vitamin D concentration	b[8]	448,31	44,56	110,58	592,67
ECP concentration	b[9]	-1544,18	152,56	-2054,95	447,95
IgE concentration	b[10]	264,73	61,80	-155,63	518,19
CC16 concentration	b[11]	-6,7805	0,7412	-9,9228	1,9798
EDN concentration	b[12]	32,8938	21,5136	-20,8711	85,0387
VCAM-1 concentration	b[13]	17,8356	1,5776	4,9701	22,5995
Severity of bronchiolitis	b[14]	-12,7018	4,3377	-35,7930	13,9095
VCAM_ECP	b[15]	1,1121	0,1650	-0,0755	2,2583
VCAM_EDN	b[16]	-3,0951	0,2694	-4,0230	0,8986
Form	kappa2	159,20	19,18	47,01	262,99

The estimates of regression coefficients for the second population show a significant impact of the following factors and markers on the risk of developing recurrent wheezing: living in a rural area β=517.8); allergic history β=679.57); passive smoking β=1114); artificial feeding β=767.3); vitamin D deficiency and insufficiency β=448,3), and elevated level of VCAM- 1 in the blood serum (β= 17.84). These factors are likely to increase the risk of recurrent wheezing in children with bronchiolitis.

Thus, testing the hypotheses using the two-population mixed Weibull survival model confirms the first hypothesis while only VCAM and EDN levels in the blood serum proved to be significant prognostic markers. The role of EDN is particularly important for making predictions, as it determines the heterogeneity of the two populations. However, the hypothesis regarding the level of VCAM in the blood serum as an important indicator of the pathogenic process that stimulates the production of ECP and EDN markers is not confirmed.

However, the hypothesis for both populations is confirmed that both a history of allergies and artificial feeding significantly increase the risk of recurrent wheezing in children with a history of bronchiolitis. The hypothesis regarding the role of passive smoking in increasing the risk of recurrent wheezing in children with bronchiolitis is only confirmed for children with an EDN level in the blood serum that does not exceed 7 ng/ml.

Given the prevalence of recurrent wheezing, the search for prognostic markers in young children with a history of bronchiolitis remains relevant.

Immune cells and molecular mediators play a significant role in the pathogenesis of inflammation in bronchiolitis, which are involved in the local inflammatory response in the airways under the influence of viruses or bacteria [19, 20]. In inflammation, leukocyte transport is regulated by the complex and coordinated actions of many molecular mediators, including chemokines, selectins, and cell adhesion molecules, including VCAM-1 [9, 21]. Oxidative stress, which develops in respiratory pathology at the systemic level, can contribute to the development of endothelial dysfunction involving VCAM-1 [22]. However, there are no reports in literature on the significance of endothelial dysfunction as a risk factor for recurrent wheezing in young children with bronchiolitis.

In our opinion, it is important to search for diagnostic markers of allergic inflammation in bronchiolitis, considering the predisposition of children with a complicated allergic history to the risk of recurrent wheezing.

The main proteins of eosinophils are ECP and EDN, which not only reflect the activity of the latter, but also increase in allergic diseases as well as other inflammatory processes [23, 24]. ECP and EDN levels may be indicative of the degree of activation of major pro-inflammatory cells in allergic inflammation and hence, indirectly, of the severity of the inflammatory process. In scientific literature, increasing attention is being given to the

determination of eosinophilic cytotoxic substances in the blood serum. Specifically, a correlation has been established between the serum levels of eosinophilic cytotoxic substances and the severity of the patient's condition in an allergic process [25].

In our study, we aimed to investigate the possible role of allergic inflammation markers (ECP and EDN) as risk factors for recurrent wheezing in young children with bronchiolitis.

Conclusions.

1. Levels of VCAM-1, ECP, and EDN in the blood serum are reliable markers for predicting recurrent wheezing in children with bronchiolitis. A level of EDN ≤ 7 ng/ml in the blood serum is a prognostic marker for the risk of recurrent wheezing in children with bronchiolitis.

2. The hypothesis that artificial feeding in children with bronchiolitis and a history of allergies confirms and significantly increases the risk of recurrent wheezing in these children. The hypothesis regarding the role of passive smoking in significantly increasing the risk of recurrent wheezing in children with bronchiolitis is only confirmed for patients with an EDN level not exceeding 7 ng/ml in the blood serum.

Prospects for further research: The conducted study complements the prognostic criteria for recurrent wheezing in young children with bronchiolitis. However, further investigation is needed to study the risk factors for recurrent wheezing in children with a history of bronchiolitis.

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АНАЛІЗ РИЗИКУ ВИНИКНЕННЯ РЕЦИДИВУЮЧОГО ВІЗИНГУ У ДІТЕЙ ХВОРИХ НА БРОНХІОЛІТ НА ОСНОВІ МАТЕМАТИЧНОЇ МОДЕЛІ ВЕЙБУЛЛА

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Резюме

Вступ. Враховуючи частоту виникнення рецидивуючого візингу (до 50 % випадків) у дітей раннього віку протягом першого року після перенесеного бронхіоліту, особливої уваги потребує оцінка прогностичної цінності діагностичних біологічних маркерів бронхіоліту.

Відповідно до сучасних уявлень, вагоме значення у патогенезі бронхіоліту відіграють опасисті клітини, еозинофіли, при дегрануляції яких спостерігається вивільнення катіонних білків (еозинофільного катіонного білка (ECP), еозинофільного нейротоксину (EDN)) та молекулярних медіаторів, а саме васкулярної молекули клітинної адгезії - 1 (VCAM-1), яка є регулятором адгезії лейкоцитів та їх трансендотеліальної міграції. Саме тому, VCAM-1, ECP та EDN обговорюються як важливі прогностичні маркери в оцінці ризику виникненні рецидивуючого візингу у дітей хворих на бронхіоліт.

Мета дослідження. Провести аналіз факторів ризику виникненні рецидивуючого візингу у дітей хворих на бронхіоліт з урахуванням алергологічного анамнезу, впливу зовнішніх факторів (пасивного тютюнопаління, місця проживання), рівнів VCAM-1, ECP, EDN у сироватці крові.

Матеріал і методи дослідження. Представлена стаття є фрагментом науково – дослідної роботи кафедри педіатрії №1 Вінницького національного медичного університету імені М.І. Пирогова на тему «Оптимізація діагностики та лікування соматичної патології у дітей», № держреєстрації 0115U007075.

Проведене клінічне обстеження 67 дітей малюкового віку. Основну групу склали 34 дітей хворих на бронхіоліт без обтяженого алергологічного анамнезу. Групу порівняння становили 33 дітей, хворих на бронхіоліт, які мали обтяжений алергологічний анамнез. Середній вік дітей основної групи становив 8,4±1,6 міс, групи порівняння – 6,2±1,4 міс. Аналітичний компонент дослідження базувався на параметричних моделях виживання (Вейбулла та генералізованої Гамма). Аналіз моделей Вейбулла проводили в пакетах статистичної аналітичної системи R для Mac OS X FAQ, Версія 3.1.0 2014-04-10, R. app 1.64 на базі платформи Mac OS X 10.9, архітектура 64-bit Intel Core i7.

Дослідження погоджено Комісією з питань біомедичної етики щодо дотримання морально-правових правил проведення медичних наукових досліджень Вінницького національного медичного університету імені М.І. Пирогова. Встановлено, що дослідження не суперечать основним біоетичним нормам і відповідають принципам відповідності основним положенням GCP (1996), Конвенції Ради Європи з прав людини і біомедицини (04.04.1997), Гельсінкської декларації. Всесвітньої медичної асоціації з етичних засад дослідження за участю людини (1964-2008) та наказ МОЗ України №690 від 23.09.2009 (зі змінами, внесеними згідно з наказом МОЗ України № 523 від 12.07.2012). Усі пацієнти були поінформовані про мету та можливі наслідки дослідницьких процедур. Усі пацієнти перед маніпуляцією підписали інформовану письмову згоду на участь у дослідженні.

Результати дослідження. Ризик рецидивуючого візингу у дітей хворих на бронхіоліт за моделлю Вейбулла становили: алергологічний анамнез (β=1,996); змішане вигодовування, і в ще більшій мірі штучне вигодовування (β=7,832 та β=8,337). Високі рівні ECP β=5,03, EDN β=0,182 та VCAM-1 β=0,0254 у сироватці крові є достовірними маркерами підвищеного ризику рецидивуючого візингу у дітей хворих на бронхіоліт. Проживання у сільській місцевості (β=-5,8) значно зменшує ризик рецидивуючого візингу у малюків хворих на бронхіоліт у порівнянні із дітьми, які проживають у міській місцевості (β= 0,0162).

Висновки. 1. Рівні VCAM-1, ECP та EDN у сироватці крові визначено достовірними маркерами прогнозу рецидивуючого візингу у дітей хворих на бронхіоліт. Рівень EDN ≤ 7 нг/мл у сироватці крові є прогностичним маркером для ризику виникненні рецидивуючого візингу у дітей хворих на бронхіоліт.

2. Гіпотеза про те, що штучне вигодовування у дітей хворих на бронхіоліт із обтяженим алергологічним анамнезом, підтверджує та достовірно підвищує ризик рецидивуючого візингу у дітей хворих на бронхіоліт. Гіпотеза про роль впливу пасивного тютюнопаління у достовірному підвищенні ризику рецидивуючого візингу у дітей хворих на бронхіоліт підтверджена лише для хворих із рівнем EDN, що не перевищує 7 нг/мл у сироватці крові.

Ключові слова: бронхіоліт; рецидивуючий візинг; бронхіальна обструкція; діти; ранній вік; математична модель; васкулярна молекула клітинної адгезії -1; еозинофільний катіонний білок; еозинофільний нейротоксин.

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