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ABSTRACT

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USE OF BACTERIAL LYSATE IN COMPLEX TREATMENT OF ACUTE BRONCHITIS COMBINED WITH EUTHYROID SICK SYNDROME IN PRESCHOOLERS

Objective. This study's objective was to determine bacterial lysate's effect on the state of humoral immunity (IgA, IgM, IgG) in preschool children with acute bronchitis in combination with euthyroid sick syndrome.

Materials and methods. We examined 135 children of preschool age (3 to 6 years) with acute bronchitis (main group) and 28 healthy children (control group). Group Ia included 45 children with acute bronchitis who were treated according to the standard scheme. Preschoolers with acute bronchitis in Group Ib (47 patients) additionally received bacterial lysate. Group IIa included 21 children with acute bronchitis and euthyroid sick syndrome (ESS) manifestations who received standard therapy. Group IIb consisted of 22 patients with acute bronchitis and ESS who received standard therapy and were additionally given an immunomodulator.

The bacterial lysate consisted of Staphylococcus aureus 6×10^9 colony-forming units (CFU), Streptococcus pyogenes 6×10^9 CFU, Streptococcus viridans 6×10^9 CFU, Klebsiella pneumoniae 6×10^9 CFU, Klebsiella ozaenae 6×10^9 CFU, Haemophilus influenzae B 6×10^9 CFU, Neisseria catarrhalis 6×10^9 CFU, Streptococcus pneumoniae 6×10^9 CFU (the latter included the following types in amount of 1×10^9 CFU each: TY1/EQ11, TY2/EQ22, TY3/EQ14, TY5/EQ15, TY8/EQ23, TY47/EQ24). The effectiveness of bacterial lysate in children with acute bronchitis and with or without ESS was determined by comparing the humoral immunity parameters (IgA, IgM, IgG) in the acute period (1 to 2 days after the onset) and convalescence period (7 to 10 days after the onset).

Levels of immunoglobulins (IgA, IgM, and IgG) were measured by solid-phase enzyme-linked immunosorbent assay. All results were statistically processed using the SPSS 26 software.

Results. No statistically significant difference was found between the values of immunoglobulins A, M, and G in children with acute bronchitis and with or without ESS manifestations in the acute period of the disease. At the same time, the above parameters were significantly higher than the corresponding values in the control group.

A statistically significant difference was observed in the humoral

immunity parameters of patients who were given the bacterial lysate vs. patients who were not.

In children who were additionally given the bacterial lysate, IgA levels practically equaled the levels of the control group in the convalescence period. The serum levels of IgM and IgG in children who additionally received the immunomodulator tended to approach the values of the control group.

Conclusions. The use of bacterial lysate positively affected the restoration of humoral homeostasis, especially on the level of immunoglobulin A, in children with acute bronchitis and with or without the euthyroid sick syndrome. The bacterial lysate demonstrated high efficiency against this disease in this group of patients.

Keywords: acute bronchitis, children, euthyroid sick syndrome, humoral immunity, immunoglobulin A, immunoglobulin M, immunoglobulin G, immunomodulator, bacterial lysate.

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РЕЗЮМЕ

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ЗАСТОСУВАННЯ БАКТЕРІАЛЬНОГО ЛІЗАТУ У КОМПЛЕКСНОМУ ЛІКУВАННІ ГОСТРОГО БРОНХІТУ У ДІТЕЙ ДОШКІЛЬНОГО ВІКУ У ПОЄДНАННІ ІЗ СИНДРОМОМ ЕУТИРЕОЇДНОЇ ПАТОЛОГІЇ

Метою цього дослідження було визначення впливу бактеріального лізату на стан гуморального імунітету (IgA, IgM, IgG) дітей дошкільного віку хворих на гострий бронхіт у поєднанні із синдромом еутиреоїдної патології.

Матеріали і методи. Нами було обстежено 135 дітей дошкільного віку (від 3 до 6 років) хворих на гострий бронхіт (основна група) і 28 здорових дітей (контрольна група). Група Іа включала 45 дітей хворих на гострий бронхіт, які лікувалися за звичною схемою. Діти хворі на гострий бронхіт з групи Іб (47 пацієнтів) додатково отримували бактеріальний лізат. До групи ІІа була включена 21 дитина, хвора на гострий бронхіт з ознаками синдрому еутиреоїдної патології (СЕП), що отримували стандартну терапію. Групу ІІб склали 22 пацієнти, хворі на гострий бронхіт у поєднанні з СЕП, до схеми лікування яких було додано імуномодулятор.

Визначення ефективності застосування бактеріального лізату, який складається з Staphylococcus aureus 6×10^9 колонієутворюючих одиниць (КУО), Streptococcus pyogenes 6×10^9 КУО, Streptococcus viridans 6×10^9 КУО, Klebsiella pneumoniae 6×10^9 КУО, Klebsiella ozaenae 6×10^9 КУО, Haemophilus influenzae B 6×10^9 КУО, Neisseria catarrhalis 6×10^9 КУО, Streptococcus pneumoniae 6×10^9 КУО (остання бактерія містить по 1×10^9 одиниць наступних типів: TY1/EQ11, TY2/EQ22, TY3/EQ14, TY5/EQ15, TY8/EQ23, TY47/EQ24, у дітей хворих на гострий бронхіт у поєднанні із СЕП та без нього, було проведено шляхом порівняння показників стану гуморального імунітету (IgA, IgM, IgG) у гострий період (1–2 день хвороби)

та період реконвалесценції (7–10 день хвороби).

Рівні імуноглобулінів (IgA, IgM та IgG) визначали методом твердофазового імуноферментного аналізу. Усі результати були статистично оброблені за допомогою пакета SPSS 26.

Результати. Між показниками імуноглобулінів A, M та G дітей хворих на гострий бронхіт з ознаками СЕП та без них у гострому періоді хвороби не виявлено статистично достовірних відмінностей. Водночас, вищезазначені показники статистично достовірно перевищують відповідні значення групи контролю.

Виявлені статистично достовірні відмінності між показниками гуморальної ланки імунітету пацієнтів після застосування бактеріального лізату та без нього.

У періоді реконвалесценції рівень показника IgA у дітей, в схему лікування яких додавали бактеріальний лізат, практично досягав рівня групи контролю. Рівень IgM та IgG у сироватці крові дітей, які додатково отримували імуномодулятор, мав тенденцію наближення до показника групи контролю.

Висновки. Застосування бактеріального лізату позитивно впливало на відновлення гуморального гомеостазу, особливо рівня імуноглобуліна А, у дітей хворих на гострий бронхіт з ознаками синдрому еутиреоїдної патології та без нього. Препарат показав свою високу ефективність при даному захворюванні у цієї групи пацієнтів.

Ключові слова: гострий бронхіт, діти, синдром еутиреоїдної патології, гуморальний імунітет, імуноглобулін A, M, G, імуномодулятор, бактеріальний лізат.

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INTRODUCTION / ВСТУП

Acute respiratory infections occupy an important place in the structure of pediatric morbidity and therefore constantly draw the attention of researchers worldwide to this medical, social, economic, and scientific problem. Acute infectious diseases of the respiratory system are the primary pathology reported in children of different age groups (up to 90%), while this indicator was several times lower among adults. Acute bronchitis is one of the widespread diseases of children, which maintains its relevance from year to year. This pathology is a frequent reason for seeking outpatient and inpatient medical help from a pediatrician. The incidence rate of acute bronchitis among children is about 100 per 1000 children [1, 2, 3, 4].

The effectiveness of a person's immune response depends on the state of the endocrine system. In this regard, the involvement of endocrine glands such as the thyroid and pituitary glands in the inflammatory process determines their role in the protective and adaptive resistance of a child's body [5, 6, 7]. As a result, subclinical changes in thyroid hormone levels often occur with infectious diseases, in particular, acute bronchitis, and the syndrome of euthyroid pathology (ESS) develops, namely its first and most common variant – "low T_3 syndrome" [8, 9, 10, 11].

According to modern views, immunomodulators are often used for the prevention and therapy of and rehabilitation after inflammatory broncho–pulmonary diseases [12, 13, 14]. Particular success at each stage was achieved with respiratory diseases in children and adults [15, 16]. In the last few decades,

bacterial lysates have attracted much attention from scientists and doctors. Based on the data obtained, this group of immunomodulators proved effective and safe in preventing and treating respiratory infectious diseases. Decreased acute and chronic non-specific respiratory disease exacerbations rates were reported. At the same time, the authors showed a reduction in the duration of antibiotic therapy for recurrent respiratory infections in children. Also, the disease duration was shorter, and the low probability of side effects of these drugs was proved [17, 18, 19, 20, 21].

Under the influence of bacterial lysates, the immune memory system is activated. Thus, when the mucosa-associated lymphoid tissue (MALT) is affected, the synthesis of secretory immunoglobulin A (sIgA) is stimulated; sIgA can agglutinate microorganisms, provide a bacteriostatic effect, reduce the adhesive properties of the endothelium, and also neutralize toxins [22]. During repeated contact with the same pathogen, the immune system responds more quickly and to a smaller amount of the pathogen due to memory B cells that synthesize a small number of antibodies over a long period of time. In addition, due to the higher affinity of these antibodies to the antigen, the secondary immune reaction is stronger and more intensive.

Such immunomodulatory effect is a very effective and reliable method of balancing immune system disorders in acute infections. Thus, we consider it is promising to study the immune response peculiarities in acute bronchitis and the possibilities of their pathogenetic correction by including the bacterial lysate in the treatment regimen.

OBJECTIVE

The study's objective was to determine the effectiveness of a bacterial lysate in preschoolers with acute bronchitis and with or without ESS. The bacterial lysate consisted of Staphylococcus aureus 6×10^9 colony-forming units (CFU), Streptococcus pyogenes 6×10^9 CFU, Streptococcus viridans 6×10^9 CFU, Klebsiella pneumoniae 6×10^9 CFU, Klebsiella ozaenae 6×10^9 CFU, Haemophilus influenzae B 6×10^9 CFU, Neisseria catarrhalis 6×10^9 CFU, Streptococcus pneumoniae 6×10^9 CFU (the latter included the following types in amount of 1×10^9 CFU each: TY1/EQ11, TY2/EQ22, TY3/EQ14, TY5/EQ15, TY8/EQ23, TY47/EQ24).

MATERIALS AND METHODS

We examined 135 children of preschool age (3 to 6 years) with acute bronchitis (main group) who underwent treatment in the infectious departments of the Municipal Non-Profit Enterprise "Saint Zinaida's Children's Clinical Hospital" of the Sumy City Council and 28 healthy children (control group) who were followed up by a primary care pediatrician at the Municipal Non-Profit Enterprise "Primary Health Care Center No. 2" of the Sumy City Council. Group Ia included 45 children with acute bronchitis who were treated according to the standard scheme. Preschoolers with acute bronchitis in Group Ib (47 patients) additionally received bacterial lysate. Group IIa included 21 children with acute bronchitis and euthyroid sick syndrome (ESS) manifestations who received standard therapy. Group IIb consisted of 22 patients with acute bronchitis and ESS, who received standard therapy and were additionally given an immunomodulator.

The effectiveness of the immunomodulator in children with acute bronchitis and with or without ESS was determined by comparing the humoral immunity parameters (IgA, IgM, IgG) in the acute period (1 to 2 days after the onset) and convalescence period (7 to 10 days after the onset).

The examination and treatment of the children included in the study were agreed with their parents (via informed consent) and complied with the bioethics principles, which was confirmed by the protocol of the Ethics Committee of the Municipal Non-Profit Enterprise "Saint Zinaida's Children's Clinical Hospital" of the Sumy City Council.

The bacterial lysate was used from the first day of hospitalization according to the regime specified in the package leaflet: 1 tablet once a day sublingually for 10 days, 1 hour before meals.

In the children of the main group, the diagnosis of acute bronchitis was verified on the basis of complaints of children and their parents, anamnesis data, objective symptoms, laboratory and instrumental examinations data, and in accordance with the Pediatric Pulmonology Clinical Protocol, approved by order of the Ministry of Health of Ukraine No. 18 dated January 13, 2005, with amendments introduced by order of the Ministry of Health of Ukraine No. 499 dated July 16, 2014 (Unified Clinical Protocol on Primary Medical Care of Acute Respiratory Infections for Adults and Children), adapted evidence-based clinical guidelines "Influenza and Acute Respiratory Infections" (2014).

The humoral immunity state was evaluated based on the levels of immunoglobulins (IgA,

IgM, and IgG) measured by a solid-phase enzyme-linked immunosorbent assay.

In addition, type 1 euthyroid sick syndrome, known as "low T_3 syndrome," was studied in children with acute bronchitis. It reflects the adaptive changes in the human body with non-thyroid diseases, which lead to subclinical changes in the serum levels of thyroid hormones in the setting of euthyroidism: low T_3 (triiodothyronine) and fT_3 (free triiodothyronine) and high rT_3 (reversible triiodothyronine).

The results obtained were statistically processed using the SPSS 26 software. Descriptive statistics and a comparison of mean values were used to characterize the course of acute bronchitis in preschool children. The differences between groups were confirmed or refuted using analysis of variance for quantitative traits and the chi-square test for nominal or ordinal variables.

RESULTS

In order to determine the effectiveness of the bacterial lysate in the treatment of acute bronchitis with or without the euthyroid sick syndrome in preschoolers, the dynamic definition of the humoral immunity parameters (IgA, IgM, IgG) was used.

No statistically significant difference was found between the values of immunoglobulins A, M, and G in children with acute bronchitis and with or without ESS manifestations in the acute period of the disease (Table 1 and Table 2).

Table 1 – Parameters of the humoral immunity in children with acute bronchitis in the acute period with or without signs of ESS

Parameter		N	Mean	Std. Deviation	Std. Error	95 % Confidence Interval for Mean	
						Lower Bound	Upper Bound
IgA, g/L	Ia	45	0.9456	0.03805	0.00567	0.9341	0.9570
	IIa	21	0.9557	0.05929	0.01294	0.9287	0.9827
	Ib	47	0.9615	0.05718	0.00834	0.9447	0.9783
	IIb	22	0.9391	0.03902	0.00832	0.9218	0.9564
	Total	135	0.9516	0.04936	0.00425	0.9432	0.9600
IgM, g/L	Ia	45	0.8438	0.01736	0.00259	0.8386	0.8490
	IIa	21	0.8490	0.01814	0.00396	0.8408	0.8573
	Ib	47	0.8432	0.01946	0.00284	0.8375	0.8489
	IIb	22	0.8509	0.02202	0.00469	0.8411	0.8607
	Total	135	0.8456	0.01907	0.00164	0.8423	0.8488
IgG, g/L	Ia	45	11.6271	0.21811	0.03251	11.5616	11.6926
	IIa	21	12.4576	0.14429	0.03149	12.3919	12.5233
	Ib	47	11.6528	0.30069	0.04386	11.5645	11.7411
	IIb	22	12.3918	0.14657	0.03125	12.3268	12.4568
	Total	135	11.8899	0.43349	0.03731	11.8161	11.9636

It is worth noting that in the acute period, the indicated parameters were significantly higher in the main group than those in the control group: IgA (0.84 ± 0.005) g/L, IgM (0.72 ± 0.003) g/L, and IgG (10.31 ± 0.08) g/L.

A statistically significant difference was observed in the humoral immunity parameters of children with regard to the bacterial lysate (Table 3 and Table 4).

As can be seen, in the period of convalescence, the levels of the IgA in the subgroups receiving standard therapy were: Ia (0.94 ± 0.005) g/L and IIa (0.95 ± 0.012) g/L, while in the subgroups receiving standard therapy + immunomodulator these values were: Ib (0.842 ± 0.002) g/L and IIb (0.843 ± 0.003) g/L, with the latter practically reaching the values of the control group (0.845 ± 0.005) g/L. The IgM levels in the subgroups receiving standard therapy were: Ia (0.8304 ± 0.0027) g/L and IIa (0.8338 ± 0.0036) g/L, while in

Table 2 – Analysis of variance for the humoral immunity parameters in children with acute bronchitis in the acute period with or without signs of ESS

Parameter		Sum of Squares	Df	Mean Square	F	Sig.
IgA, g/L	Between Groups	0.010	3	0.003	1.385	0.250
	Within Groups	0.316	131	0.002		
	Total	0.326	134			
IgM, g/L	Between Groups	0.001	3	0.000	1.189	0.317
	Within Groups	0.047	131	0.000		
	Total	0.049	134			
IgG, g/L	Between Groups	18.061	3	6.020	110.775	0.0713
	Within Groups	7.120	131	0.054		
	Total	25.181	134			

Df = number of degrees of freedom
F = estimated F-test value
Sig. = statistical significance

Table 3 – Parameters of the humoral immunity in children with acute bronchitis in the convalescence period with or without signs of ESS depending on the therapy

Parameter		N	Mean	Std. Deviation	Std. Error	95 % Confidence Interval for Mean	
						Lower Bound	Upper Bound
IgA, g/L	Ia	45	0.9404	0.03630	0.00541	0.9295	0.9514
	IIa	21	0.9455	0.05539	0.01239	0.9196	0.9714
	Ib	47	0.8417	0.01508	0.00220	0.8373	0.8461
	IIb	22	0.8432	0.01524	0.00325	0.8364	0.8499
	Control group	28	0.8450	0.02411	0.00456	0.8356	0.8544
	Total	163	0.8827	0.05734	0.00451	0.8738	0.8916
IgM, g/L	Ia	45	0.8304	0.01833	0.00273	0.8249	0.8360
	IIa	21	0.8338	0.01658	0.00362	0.8263	0.8414
	Ib	47	0.7306	0.01881	0.00274	0.7251	0.7362
	IIb	22	0.7612	0.01810	0.00386	0.8288	0.8448
	Control group	28	0.7243	0.01597	0.00302	0.7181	0.7305
	Total	163	0.7761	0.05525	0.00433	0.7762	0.7933
IgG, g/L	Ia	45	11.3538	0.23753	0.03541	11.2824	11.4251
	IIa	21	12.1195	0.30662	0.06691	11.9800	12.2591
	Ib	47	10.2860	0.13875	0.02024	10.2452	10.3267
	IIb	22	10.4891	0.41484	0.08844	10.3052	10.6730
	Control Group	28	10.3132	0.42795	0.08087	10.1473	10.4792
	Total	163	10.8491	0.72418	0.05672	10.7371	10.9611

the subgroups receiving standard therapy + immunomodulator, these values were: Ib (0.7306 ± 0.0027) g/L and IIb (0.7612 ± 0.006) g/L, with the latter tending to reach the values of the control group (0.72 ± 0.003) g/L. The IgG levels in the blood serum of subgroups receiving standard therapy were: Ia (11.3538 ± 0.0354) g/L and IIa (12.1195 ± 0.0669) g/L, while in the subgroups receiving standard therapy + immunomodulator, these values were: Ib (10.286 ± 0.02024) g/L and IIb (10.4891 ± 0.08844) g/L, with the latter tending to reach the values of the control group (10.3132 ± 0.0809) g/L.

Table 4 – Analysis of variance for the humoral immunity parameters in children with acute bronchitis in the convalescence period with or without signs of ESS depending on the therapy

Parameter		Sum of Squares	Df	Mean Square	F	Sig.
IgA, g/L	Between Groups	0.382	4	0.096	101.791	0.000
	Within Groups	0.147	157	0.001		
	Total	0.529	161			
IgM, g/L	Between Groups	0.444	4	0.111	348.563	0.000
	Within Groups	0.050	158	0.000		
	Total	0.494	162			
IgG, g/L	Between Groups	71.152	4	17.788	203.556	0.000
	Within Groups	13.807	158	0.087		
	Total	84.959	162			

Df = number of degrees of freedom
F = estimated F-test value
Sig. = statistical significance

DISCUSSION

Modern medical literature provides a large number of works devoted to studying the effectiveness of immunomodulators such as bacterial lysates.

In the course of the study, this bacterial lysate's high efficiency was proven to prevent exacerbations and relapses of rhinosinusitis in children. Immunoprophylaxis was effective in 70% of patients, as evidenced by the normalization of IgA, IgM, α-IFN, and circulating immune complexes levels [23].

Other researchers described the positive effect of the immunomodulator on the levels of IgA and IgG in oropharyngeal secretions of patients with chronic tonsillitis and type 1 diabetes [24].

Several authors reported an increase in serum and secretory IgA, serum IgG, and a decrease in serum IgE in patients with bronchial asthma after taking bacterial lysates [25].

In addition, some data confirm the reasonability of immunomodulator use in respiratory tract infections due to their influence on innate and acquired immune response mechanisms, providing both immunoglobulin-bound and cell-mediated immunity. Due to their immunoregulatory effects, they can reduce inflammation and hyperreactivity [26].

Moreover, by stimulating non-specific mechanisms of immune protection (increased IgA and interferon-γ levels), bacterial lysates can influence the production of specific antibodies against bacterial antigens that are part of the drug [27].

CONCLUSIONS / ВИСНОВКИ

Thus, the use of bacterial lysate in children with acute bronchitis positively affected the restoration of the patient's immunological homeostasis, as evidenced by the humoral immunity parameters before and after treatment. In children who were additionally given the immunomodulator, IgA levels practically equaled the levels of the control group in the convalescence period, while the IgM and IgG levels tended to approach the values of the control group. The drug showed high effectiveness against this disease in patients with or without the signs of the euthyroid sick syndrome. The data obtained during the study indicate the need to include the immunomodulator in the complex treatment of acute bronchitis in preschool children, which is justified pathogenetically and will contribute to the effectiveness of treatment.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Prospects for further research are to expand the study of immunomodulators' influence on various parameters of the immunological status in children with acute bronchitis and to search for the optimal combination of drugs. This will make it possible to more accurately understand the pathogenetic processes of the disease development, as well as the peculiarities of the child's body response to the administered drug, and as a result, to increase the effectiveness of treatment in children with acute bronchitis with or without the euthyroid sick syndrome.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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None.

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