

ХАРАКТЕРИСТИКА ИММУНОКОМПЕТЕНТНЫХ КЛЕТОК У ДЕТЕЙ С АЛЛЕРГЕН-ИНДУЦИРОВАННЫМ ФЕНОТИПОМ БРОНХИАЛЬНОЙ АСТМЫ ПРИ ТЕРАПИИ ГЛЮКОЗАМИНИЛМУРАМИЛДИПЕПТИДОМ

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Резюме. Цель: изучение динамики количественных показателей и функциональной активности иммунокомпетентных клеток при применении глюкозаминилмурамилдипептида у детей с аллерген-индуцированным фенотипом бронхиальной астмы.

Проведен комплексный анализ показателей врожденного и адаптивного иммунитета у 60 детей с аллерген-индуцированной бронхиальной астмой (БА) средней тяжести клинического течения в возрасте 3-11 лет и у 30 здоровых сверстников. Верификация фенотипа БА проводилась в соответствии с международным согласительным документом PRACTALL (2008). Критерии исключения из исследования: тяжелое течение БА и иммунокорригирующая терапия в предшествующие 6 месяцев. В проспективном параллельном открытом исследовании изучали влияние глюкозаминилмурамилдипептида на характеристики иммунокомпетентных клеток в течение трех месяцев с разделением на две группы сравнения методом случайной выборки в зависимости от проводимой терапии. В венозной крови оценку клеток проводили на проточном цитофлюориметре COULTER EPICS XL фирмы Beckman Coulter Inc. Иммуноферментным методом определяли уровни цитокинов реактивами R&D Diagnostics Inc (США) и IgE-реагентами «Компания Алкор Био» (Санкт-Петербург), продукцию цитокинов исследовали реагентами «Вектор-Бест» (г. Новосибирск). Статистическая обработка с использованием программы Statistica 10 с критическим уровнем значимости $p < 0,05$, исследование связей коэффициентом ранговой корреляции Спирмена, многомерный корреляционный анализ с построением плеяд по В.П. Терентьеву (1959) и проверку нормальности распределения значений признака (Shapiro–Wilk). Объем выполненных исследований позволил оценить результаты с достоверностью 95-99%.

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Изменения в системе адаптивного реагирования у детей с аллерген-индуцированным фенотипом БА характеризовались усилением пролиферации, угнетением процессов негативной регуляции, активацией синтеза цитокинов Th2-профиля, усилением синтеза IgE.

Выявлены нарушения обеспеченности, функциональной активности иммунокомпетентных клеток и продукции цитокинов сохранялись при терапии ингаляционными глюкокортикоидными препаратами с усугублением снижения синтеза IFN γ .

Применение при БА у детей глюкозамурамилдипептида обеспечивало снижение спонтанной и митоген-индуцированной продукции IL-4 и коррекцию девиации структурно-функциональных характеристик иммунокомпетентных клеток.

Включение глюкозаминилмурамилдипептида в схемы лечения аллерген-индуцированного фенотипа астмы у детей обеспечило нормализацию показателей клеточного звена иммунитета, коррекции дисбаланса Th1/Th2-лимфоцитов, повышение активности Th1, адекватную спонтанную и индуцированную продукцию IFN γ клетками периферической крови

Ключевые слова: иммунокомпетентные клетки, глюкозаминилмурамилдипептид, аллерген-индуцированная бронхиальная астма, дети

CHARACTERISTICS OF IMMUNOCOMPETENT CELLS IN CHILDREN WITH ALLERGEN-INDUCED PHENOTYPE OF BRONCHIAL ASTHMA TREATED WITH GLUCOSEMINYLMURAMILDIPEPTIDE

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Abstract. Purpose: to study the changes in quantitative values and functional activity of immunocompetent cells on application of glucoseminylmuramildipeptide in children with allergen-induced phenotype of bronchial asthma.

We have performed an integrated assessment of parameters of innate and acquired immunity in 60 children at the age of 3-11 years old with allergen-induced bronchial asthma (BA) with mild clinical course of disease, and in 30 healthy children of the same age. BA phenotypes were verified in accordance with PRACTALL international consensus report (2008). Study exclusion criteria were: severe course of bronchial asthma and application of immunocorrecting therapy during preceding six months. We conducted a prospective parallel open study of the effect of glucoseminylmuramildipeptide on the parameters of immunocompetent cells during three months with division into two control groups by random sampling technique on the basis of therapy being performed. To analyze the venous blood cells, we used flow cytofluorometer COULTER EPICS XL by Beckman Coulter Inc. Cytokine levels were determined using immunoenzyme method with reagents by R&D Diagnostics Inc (USA) and IgE – with reagents by Alkor Bio Company (St. Petersburg), production of cytokines – using reagents by Vektor-Best (Novosibirsk). Statistical processing of data was performed using Statistica 10 program with significance level $p < 0.05$, assessment of correlations by Spearman correlation analysis, multidimensional correlation analysis with V.P. Terentyev's method of correlation pleiades (1959) and testing for normal distribution of characteristic values (Shapiro–Wilk). The scope of our study permitted to evaluate its findings with accuracy 95-99%.

The changes of the adaptive response system in children with allergen-induced phenotype of BA were characterized by the intensified proliferation, suppression of negative regulation processes, activation of synthesis of Th2-profile cytokines, and intensified synthesis of IgE.

The identified impairments of availability, functional activity of immunocompetent cells and cytokine production were preserved in application of inhaled corticosteroids therapy, with further decreasing of IFN γ synthesis.

Application of glucosaminilmuramildipeptide in children with BA provided for reduction of spontaneous and mitogen-induced production of IL-4 and correction of deviated structural and functional characteristics of immunocompetent cells.

Incorporation of glucosaminilmuramildipeptide into therapeutic regimens for allergen-induced phenotype of BA in children promoted normalization of parameters of the cellular component of immune system, amelioration of Th1/Th2-imbalance, increase of Th1 activity, and adequate spontaneous and induced production of IFN γ by peripheral blood cells.

Keywords: immunocompetent cells, glucosaminilmuramildipeptide, allergen-induced bronchial asthma, children

Introduction

Immunological indicators reflect the body response to the action of physiological or pathological factors, immunological activation or exhaustion [2]. Pathogenic mechanism of allergic diseases involves imbalance of immune system functioning and impairments of quantitative availability and functional activity of immunoregulatory cells [1, 8].

Chronic nature of inflammation, heterogeneity of pathogenetic mechanisms and clinical forms of bronchial asthma, variability of response to anti-inflammatory and immunotropic therapy dictate the urgent need for optimization of therapeutic regimens in accordance with immune mechanisms underlying various phenotypes of the disease [6, 8, 12, 15].

The ability of immunocompetent cells to demonstrate effector properties, including synthesis of cytokines, secretory degranulation, release of channel-forming proteins and granzymes, is characterized by cells' maturity or lineage stage [10, 13].

Scope of activity of immunocompetent cells and cytokine profile regulates the type of inflammation and phenotype of the disease and influences the efficiency of anti-inflammatory therapy in patients with bronchial asthma [1, 4, 8].

Group of critical factors for the development of BA-phenotypes includes cytokine dysregulation and imbalance of cellular profile of immune response [4, 6].

Pathogenetic significance of immune and cytokine mechanisms in allergic inflammation determine the information value and importance of monitoring of immunological indicators in the course of immunotropic therapy for bronchial asthma [3, 7, 9].

Purpose: to study the changes in quantitative values and functional activity of immunocompetent cells on application of glucosaminilmuramildipeptide in children with allergen-induced phenotype of bronchial asthma.

The tasks of the study were to analyze the immune mechanisms of allergen-induced phenotype of bron-

chial asthma in children and to monitor the parameters of immunocompetent cells during incorporation of glucosaminilmuramildipeptide into therapeutic regimen.

The study was conducted in Federal State Budgetary Educational Institution of Higher Education "Pacific State Medical University" of the Ministry of Healthcare of the Russian Federation (President V.B. Shumatov), design of the study was approved by the Interdisciplinary Ethics Committee, and informed consents were signed by parents.

Materials and methods

The enrolled patients were 90 children at the age of 3-11 years old, of which 60 children had the verified diagnosis of allergen-induced phenotype of bronchial asthma (BA) with mild clinical course of disease, and 30 were healthy children of the same age.

Diagnosis and phenotype of BA were verified in the City Centre for Allergic and Respiratory Diseases of Regional State Budgetary Healthcare Institution "Vladivostok Clinical and Diagnostic Centre" (Chief Medical Officer A.A. Kabieva) in accordance with recommendations of the international consensus document PRACTALL (The European Pediatric Asthma Group Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report) by European Academy of Allergy and Clinical Immunology and the American Academy of Allergy [4]. In verification of the diagnosis, hereditary history and case history were taken into account, and allergological assessment was performed (skin testing, determination of total and specific IgE in blood serum). The group of healthy children of the same age was under care of the Health Centre of Regional State Budgetary Healthcare Institution "Vladivostok Clinical and Diagnostic Centre".

Study exclusion criteria were: age below 3 or over 11 years old, acute respiratory disease, mild or severe course and/or exacerbation of bronchial asthma, presence and/or application of immunocorrecting drugs during preceding six months. Clinical laboratory

study was conducted in the Department of Clinical Laboratory Diagnostics, General and Clinical Immunology of Federal State Budgetary Educational Institution of Higher Education "Pacific State Medical University" of the Ministry of Healthcare of the Russian Federation and in the immunology laboratory of the Regional Clinical Centre for Prevention and Control of AIDS and Infectious Diseases of the Regional State Budgetary Healthcare Institution "Regional Clinical Hospital No. 2" (Head S.P. Kruglyak).

To analyze the immunological indicators, venous blood was used. To analyze leucocyte count, lymphocyte subpopulations and processes of activation in the peripheral blood cells, we used multiparameter flow cytometer COULTER EPICS XL by Beckman Coulter Inc, sample preparation stations Coulter Prep Plus and Coulter TO-prer with selection of panels of monoclonal antibodies with multicoloured combination of fluorochromes. For immunophenotyping, fluorescent particles Flow Count were used. We identified the lymphocyte populations and subpopulations, such as: T-cells, T-helpers, T-cytotoxic, regulatory index, B-cells, natural killers (NK-cells), cytolytic T-cells (NKT-cells) and activated T- and B-cells (CD3⁺CD19⁻, CD3⁺CD95⁺, CD3⁺CD4⁺, CD3⁺CD8⁺, CD4⁺CD8⁺, CD3⁻CD19⁺, CD3⁻CD16⁺CD56⁺, CD3⁺CD16⁺CD56⁺, CD3⁺CD25⁺, CD3⁺HLA-DR⁺, CD3⁺HLA-DR⁻). The results were counted as a percentage of positive cells and in absolute values. Spontaneous and mitogen-induced production of IL-4 and IFN γ by peripheral blood cells was evaluated using CYTOKINE-STIMUL-BEST sets by Vektor-Best JSC (Novosibirsk). Total and specific IgE content was measured in IU/ml by enzyme linked immunosorbent assay using reagent kits by Alkor Bio Company Ltd. (St. Petersburg).

The object of study was the effect of glucose-minylmuramildipeptide on the parameters of immunocompetent cells in children with allergen-induced phenotype of bronchial asthma within the scope of prospective parallel open study with division into two control groups comparable in gender and age using random sampling technique on the basis of therapy. The patients from the first group (n = 30) were receiving basic anti-inflammatory therapy with inhaled corticosteroids, and in the second group (n = 30) such basic therapy with inhaled corticosteroids was combined with application of glucoseminylmuramildipeptide (Licopide – Peptek JSC, Russia) at a dose of 1 mg once daily for 10 days, three courses per month.

For statistical processing of numerical data, we used descriptive, parametric and non-parametric statistic

methods of "Statistica 10" program with calculation of: arithmetical mean (M), standard deviation (σ), standard error of the mean ($\pm m$), confidence interval (CI), indicator confidence factor (t) and differences (t and p) with significance level $p < 0.05$. Correlations (r – correlation coefficient) were analyzed using Spearman correlation analysis, multidimensional correlation analysis with V.P. Terentyev's method of correlation *pleiades* (1959) and testing for normal distribution of characteristic values (Shapiro–Wilk). The scope of our study permitted to evaluate its findings with accuracy 95-99%.

Results and discussion

The undertaken study of structural and functional characteristics of immunocompetent cells showed presence of differences in availability and functional activity of the parameters being studied in children with allergen-induced phenotype of bronchial asthma as compared to the same of healthy children of the same age. Absolute lymphocyte count and absolute T-lymphocyte count in children with BA is significantly lower than the same in healthy children ($2.59 \pm 0.18 \cdot 10^9/L$ against $3.37 \pm 0.18 \times 10^9/L$, at $p < 0.05$ and $1,996.7 \pm 88.95$ cells/ μL against $2,356.90 \pm 126.95$ cells/ μL , at $p < 0.05$); they have stronger expression of CD3⁺CD25⁺ activation markers than healthy children (203.5 ± 18.03 cells/ μL against 137.45 ± 4.67 cells/ μL , at $p < 0.01$) and low absolute B-lymphocyte count (433.5 ± 24.58 cells/ μL against 548.59 ± 41.31 cells/ μL , at $p < 0.05$).

The findings of the study are coherent with the reported information that chronic inflammatory process during bronchial asthma is accompanied with intensification of synthesis of biologically active substances which have an effect on the lymphocytes' receptor system, resulting in change of the level of their functional capacities [9, 13].

We registered the intensification of expression of T-lymphocyte activation marker HLA-DR⁺B in the group of children with allergen-induced phenotype of bronchial asthma ($2.20 \pm 0.20\%$ and 61.6 ± 6.11 cells/ μL against $1.10 \pm 0.24\%$ and 46.01 ± 11.96 cells/ μL in the group of healthy children of the same age, respectively at $p < 0.05$). Number of lymphocytes with apoptosis marker CD3⁺CD95⁺ on their surface is significantly lower than in control group ($2.62 \pm 0.34\%$ against $6.10 \pm 0.26\%$, respectively at $p < 0.01$). Children with BA also demonstrated high concentration of T-lymphocytes with early activation marker (CI $162.48-215.79$ cells/ μL), deficit of T-lymphocytes ($1,902.83 \pm 112.39$ cells/ μL), T-helpers (953.42 ± 58.12 cells/ μL) and B-lymphocytes (412.92 ± 34.35 cells/ μL). Also, we recorded in this group the following average positive correlations: between the

ТАБЛИЦА 1. ДИНАМИКА СТРУКТУРНО-ФУНКЦИОНАЛЬНЫХ ХАРАКТЕРИСТИК ИММУНОКОМПЕТЕНТНЫХ КЛЕТОК У ДЕТЕЙ ПРИ РАЗЛИЧНЫХ ПРОГРАММАХ ТЕРАПИИ АЛЛЕРГЕН-ИНДУЦИРОВАННОГО ФЕНОТИПА БА ($M \pm m$; p)

TABLE 1. DYNAMICS OF STRUCTURAL AND FUNCTIONAL CHARACTERISTICS OF IMMUNOCOMPETENT CELLS IN CHILDREN WITH VARIOUS TREATMENT PROGRAMS FOR ALLERGEN-INDUCED BA PHENOTYPE ($M \pm m$; p)

No.	Indicators/unit of measure	Therapy program				
		IGKS		IGCS with glucosaminylmuramyl dipeptide		
		Before treatment	Three months of therapy	Before treatment	Three months of therapy	
1	T-lymphocytes CD3 ⁺ CD19 ⁺	%	74.56 \pm 0.62	73.15 \pm 0.80 $p > 0.05$	71.21 \pm 0.87	68.0 \pm 1.13 $p < 0.05$
		C/mkl	1996.70 \pm 88.95	1905.60 \pm 114.61 $p > 0.05$	1675.50 \pm 71.06	1503.10 \pm 89.23 $p > 0.05$
2	T-helpers CD3 ⁺ CD4 ⁺	%	39.91 \pm 0.73	39.29 \pm 0.83 $p > 0.05$	36.57 \pm 0.98	43.62 \pm 0.90 $p < 0.001$
		C/mkl	1061.10 \pm 46.46	1043.95 \pm 44.39 $p > 0.05$	956.85 \pm 36.43	1137.65 \pm 61.19 $p < 0.05$
3	T-cytotoxic CD3 ⁺ CD8 ⁺	%	27.085 \pm 0.710	27.35 \pm 0.67 $p > 0.05$	28.5 \pm 0.96	34.69 \pm 1.47 $p < 0.001$
		C/mkl	634.10 \pm 058.66	625.40 \pm 52.79 $p > 0.05$	718.90 \pm 49.22	916.70 \pm 61.29 $p < 0.05$
4	T-lymphocytes activated CD3 ⁺ CD25 ⁺	%	7.46 \pm 0.33	7.20 \pm 0.32 $p > 0.05$	7.26 \pm 0.27	6.92 \pm 0.39 $p > 0.05$
		C/mkl	203.50 \pm 18.03	186.60 \pm 17.54 $p > 0.05$	164.65 \pm 9.06	159.95 \pm 14.97 $p > 0.05$
5	CD3 ⁺ /HLA-DR ⁺	%	2.20 \pm 0.20	2.02 \pm 0.21 $p > 0.05$	3.41 \pm 0.24	2.87 \pm 0.27 $p > 0.05$
		C/mkl	61.60 \pm 6.11	57.42 \pm 6.32 $p > 0.05$	95.31 \pm 6.67	72.00 \pm 5.72 $p < 0.05$
6	B-lymphocytes CD3 ⁺ CD19 ⁺	%	13.16 \pm 0.56	13.34 \pm 0.53 $p > 0.05$	14.87 \pm 0.64	12.93 \pm 0.77 $p > 0.05$
		C/mkl	433.50 \pm 24.58	438.15 \pm 23.54 $p > 0.05$	349.75 \pm 21.52	279.05 \pm 25.84 $p < 0.05$
7	Cytolytic NK-cells CD3 ⁺ /CD16 ⁺ /CD56 ⁺	%	9.28 \pm 0.35	8.95 \pm 0.33 $p > 0.05$	11.33 \pm 1.09	13.73 \pm 0.97 $p > 0.05$
		C/mkl	296.20 \pm 13.55	285.55 \pm 12.42 $p > 0.05$	274.10 \pm 31.75	318.73 \pm 0.77 $p > 0.05$
8	Cytolytic NKT-cells CD3 ⁺ /CD16 ⁺ CD56 ⁺	%	5.54 \pm 0.53	5.53 \pm 0.52 $p > 0.05$	6.09 \pm 0.42	7.75 \pm 0.65 $p < 0.05$
		C/mkl	179.15 \pm 28.56	172.00 \pm 25.71 $p > 0.05$	141.30 \pm 14.37	193.91 \pm 8.89 $p < 0.05$

Note. $M \pm m$ is the average and average error, p is the confidence coefficient of differences in indicators in the study groups.

quantity of neutrophils and leucocytes; between the quantity of cytotoxic T-lymphocytes and activated B-lymphocytes; between the quantity of T-lymphocytes and T-helpers and the level of induced production of $\text{IFN}\gamma$, natural killers and activated T-lymphocytes. We also identified the reverse correlation between the quantity of T-lymphocytes, natural killers and T-lymphocytes with late activation markers.

The differences in functional activity of T-lymphocytes in children with allergen-induced phenotype of the disease and in the group of healthy children are illustrated with immune response imbalance, activation of antigen recognition regulation, induction of immune responsiveness, and proliferation and differentiation of lymphocytes.

Correlation analysis of structural and functional characteristics of immunocompetent cells and cytokine production with formation of pleiads in accordance with P. Terentyev's method revealed the differences in the scope, strength and direction of interrelations between the immune response links in the groups of healthy children and children with allergen-induced bronchial asthma.

One of mechanisms of BA pathogenesis is imbalance of cytokines of various T-helper profiles, in particular, $\text{IFN}\gamma$ and IL-4, which characterize the immune response polarization of Th1 and Th2 inflammation type [2, 7]. $\text{IFN}\gamma$ regulates the differentiation of naive CD4^+ -cells into Th1 and inhibits the proliferation of Th2 [7, 9]. Average levels of spontaneous production of $\text{IFN}\gamma$ and IL-4 in children with allergen-induced phenotype were equal to 8.07 ± 1.42 pg/ml and 5.04 ± 0.08 pg/ml, after mitogen induction – to 16.38 ± 1.77 pg/ml and 13.15 ± 1.21 pg/ml.

The identified stable changes in availability, functional activity of immunocompetent cells, in the adaptive response system, in proliferation with disturbance of negative regulation processes, persisting against the background of application of inhaled corticosteroids, justify the introduction of glucoseminylmuramildipeptide into therapeutic regimen for allergen-induced phenotype of BA in children.

The immunological efficiency of immunotropic drug was evaluated on the basis of monitoring of quantitative values and functional activity of immunocompetent cells before and after treatment for three months within the scope of parallel open prospective study with random division into subgroups in accordance with therapy being performed.

During the observation period, no amelioration of immune imbalance was identified in the children with allergen-induced BA undergoing therapy with inhaled corticosteroids.

While analyzing the changes of immunological indicators in children with allergen-induced BA during application of glucoseminylmuramildipeptide, we registered normalization of the quantity of eosinophiles, leucocytes, lymphocytes, neutrophil granulocytes and the number of T-helpers, T-cytotoxic lymphocytes and cytolytic NKT-cells, as well as decrease of absolute B-lymphocyte number. Introduction of glucoseminylmuramildipeptide into therapeutic regimen for BA provided for normalization of differential white blood cell count, T-lymphocytes availability and activation processes, and balance of T-cytotoxic and cytolytic NKT-cells (Table 1).

In application of the therapy with inhaled corticosteroids, no changes in spontaneous production of $\text{IFN}\gamma$ by peripheral blood cells were registered (from 7.75 ± 0.28 pg/ml to 7.15 ± 0.28 pg/ml at $p > 0.05$). We also registered suppression of induced production of $\text{IFN}\gamma$ (from 12.03 ± 0.67 pg/ml to 8.41 ± 0.40 pg/ml at $p > 0.05$); continued imbalance of spontaneous and induced production of IL-4 (from 4.94 ± 0.26 pg/ml to 4.88 ± 0.23 pg/ml at $p > 0.05$ and from 11.97 ± 0.64 pg/ml to 11.89 ± 0.52 pg/ml at $p > 0.05$). Therapy with glucoseminylmuramildipeptide provided for activation of spontaneous and mitogen-induced production of $\text{IFN}\gamma$ by peripheral blood cells (from 7.31 ± 0.34 pg/ml to 8.97 ± 0.47 pg/ml at $p < 0.01$ and from 11.37 ± 0.90 pg/ml and 15.34 ± 0.90 pg/ml at $p < 0.05$), normalization of IL-4 production ($p < 0.01$), correction of structural and functional impairments of immune response and adequate production of opposite cytokines.

As was earlier reported, the immunotropic effects of glucoseminylmuramildipeptide include intensification of macrophages' activity, activation of T-cells and B-cells, and in combination with basic anti-inflammatory therapy in patients with BA increase of allergen tolerance and stimulation of immunity are observed. One of significant immunotropic effects of glucoseminylmuramildipeptide as a part of therapy for asthma is changing of the profile of cytokines being synthesized from pro-inflammatory allergic one (IL-4, $\text{TNF}\alpha$, IL-5) to anti-inflammatory ($\text{IFN}\gamma$, IL-2), most probably, due to stimulation of Th1 as opposed to Th2 [14].

Study of immunopathogenetic peculiarities of inflammation in the realization of allergen-induced phenotype of bronchial asthma creates the necessary prerequisites for personalized selection of immunotropic therapy which allows increasing the level of disease control [3, 5, 7, 11].

In their studies, N.D. Titova et al. (2017) reported that introduction of glucoseminylmuramildipeptide into the regimen of basic anti-inflammatory therapy for BA resulted in activation of immune response,

amelioration of cytokine production imbalance and increase of allergen tolerance [14].

Conclusion

Our studies revealed the pathogenetic role of immune disorders in the realization of allergen-induced phenotype of bronchial asthma. The identified peculiarities of immunopathogenesis are important for evaluation of inflammatory reaction, determination of severity and prognosis of the disease and serve as additional criteria for customization of anti-inflammatory and immunotropic therapy.

Allergen-induced phenotype of BA is characterized with stable changes in the adaptive response system, in proliferation with disturbance of negative regulation processes.

The peculiarities of immunopathogenesis of allergen-induced BA in children justify the need for customization in the selection of immunotropic therapy with due regard to the immune mechanisms of realization of the disease phenotype and permit to recommend application of glucosaminylmuramildipeptide.

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