



## CYTOKINE PROFILE IN THE DYNAMICS OF INCREASING SEVERITY IN RECURRENT APHTHOSIS STOMATITIS

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**Relevance.** A number of studies have been carried out in Uzbekistan related to improving the diagnosis, treatment and improvement of the system for predicting, preventing and treating oral diseases in patients with chronic hepatitis B (Daminova Sh.B., 2018); the mechanism of clinics for the pathogenetic treatment of lichen planus of the oral mucosa was developed (Shukurova U.A., 2017; 2018); improved etiopathogenetic treatment of candidiasis of the oral mucosa (Yusupalikhodzhaeva S.Kh., 2019); however, a pathogenetic method for the treatment of chronic recurrent aphthous stomatitis has not been developed.

Recurrent aphthous stomatitis (RAS) refers to diseases in the formation of which the leading role is given to immunological disorders. Cytokines, being regulators of intercellular interactions, take part in the formation of the immune response [6, 7, 9, 11, 12].

Currently, there are convincing data on the role of an imbalance of

pro/anti-inflammatory mediators in maintaining and regulating the activity of the inflammatory process at the local and systemic levels [8, 13, 14, 19].

The balance of pro/anti-inflammatory cytokines determines the intensity of local manifestations of inflammatory-erosive lesions, the severity and intensity of cellular immunity, and the activity of protection against infection [20, 21, 22, 23]. This determined the need to study the concentration of pro-inflammatory TNF- $\alpha$ , IL-1 $\beta$  and anti-inflammatory IL-10 cytokines in the dynamics of increasing severity of ASD.

### **Materials and methods**

In 2021-2022 the control group of patients undergoing treatment at the polyclinic of the Tashkent State Dental Institute was 40 healthy people.

The subject of the study consisted of mixed saliva and blood serum for immunological (immunoglobulins and cytokines) and biochemical (LPO-AOS products; markers of allergic



reactions) studies in the process of diagnosis and treatment of recurrent aphthous stomatitis.

Research methods. The study used clinical, biochemical, immunological and statistical research methods. The scientific novelty of the study is as follows: the association of the severity of the course of the RAS disease with the prevalence of comorbid pathology, which can not only initiate local and systemic immunometabolic changes, but also pseudo-allergic reactions, has been proven;

a new concept of the pathogenesis of recurrent aphthous stomatitis is substantiated, according to which, along with immunological changes, increased proteolysis, pro-inflammatory cytokinemia, and an increase in lipid peroxidation products, adhesion molecules and indicators of pseudo-allergic load play an important role in the formation of the severity of the disease;

for the first time, a new method of treatment has been developed, including, combined with basic therapy, the differentiated use of antihistamines with different pharmacological directions depending on the severity of the course of the disease;

pathogenetically

substantiated criteria for the severity of the course of the disease and the effectiveness of treatment were determined, including the levels of adhesion molecules, histamine and the enzyme counteracting histamine diamine oxidase;

developed a new complex method for the treatment of recurrent aphthous stomatitis at the local (mixed saliva) and systemic (blood serum) levels.

The practical results of the study are as follows: the introduction of modern methods for diagnosing recurrent aphthous stomatitis in clinical practice has made it possible to conduct a number of screening studies in Uzbekistan;

this allowed for a detailed assessment of the pathologies of the gastrointestinal tract, kidneys and vascular system in the process of systemic inflammation;

early diagnosis of recurrent aphthous stomatitis allows not only to completely cure the patient, avoid complications, but also to assess the low effectiveness of traditional treatment.

The reliability of the results of the study is confirmed by the use of modern theoretical methods and

approaches in the scientific study, methodologically correct studies, a sufficient number of patients; using modern methods, based on complementary clinical, biochemical, immunological and statistical methods, features of the development of pathogenetic therapy for recurrent aphthous stomatitis. The results of foreign and domestic studies were also compared, the conclusions and the results obtained were confirmed by the authorized structures.

Scientific and practical significance of the research results. The theoretical significance of the study results lies in a significant enrichment of knowledge on the evaluation of clinical and dental studies, the results of studying various background somatic pathologies, early diagnosis, pathogenetic mechanisms for the prevention and treatment of chronic recurrent aphthous stomatitis, IL-4 and IL-10 concentrations, with a decrease in the number of anti-inflammatory mediators there is an increase in the concentration of pro-inflammatory cytokines.

### **Research results**

From the anamnesis of the research results, it is clear that the maximum concentrations of the studied

cytokines are found in mixed saliva, which is clinically justified and reflects the features of the cytokine regulation of cellular relationships, since cytokines are produced and exhibit maximum activity at the local level [8, 15, 16, 17, 18, 19].

It should be noted that with increasing severity of ASD, the concentrations of pro-inflammatory mediators steadily increased in all studied biological fluids.

Thus, the concentration of TNF- $\alpha$  increased in the oral fluid with mild RAS - by 105.79% ( $p < 0.01$ ); with moderate course - 247.38% ( $p < 0.01$ ) and with severe course - by 441.02% ( $p < 0.01$ ); similar dynamics in blood serum was less intense and amounted to 41.55%, respectively ( $p < 0.05$ ); 95.07% ( $p < 0.01$ ) and 168.31 ( $p < 0.01$ ) (table 1 and fig.1).

TNF- $\alpha$  is an intense pro-inflammatory mediator and, as a result, edema. It is under the influence of TNF- $\alpha$  that the secretion of other pro-inflammatory mediators is stimulated and the number of leukocytes increases.

The pro-inflammatory cytokine IL-1 $\beta$  promotes the production of adhesion molecules activated by the endothelium, is the main indicator of local inflammation, and its

accelerated formation leads to tissue destruction [2, 5, 24].

**Table 1**

The concentration of cytokines in the studied biological fluids in the dynamics of increasing severity of ASD

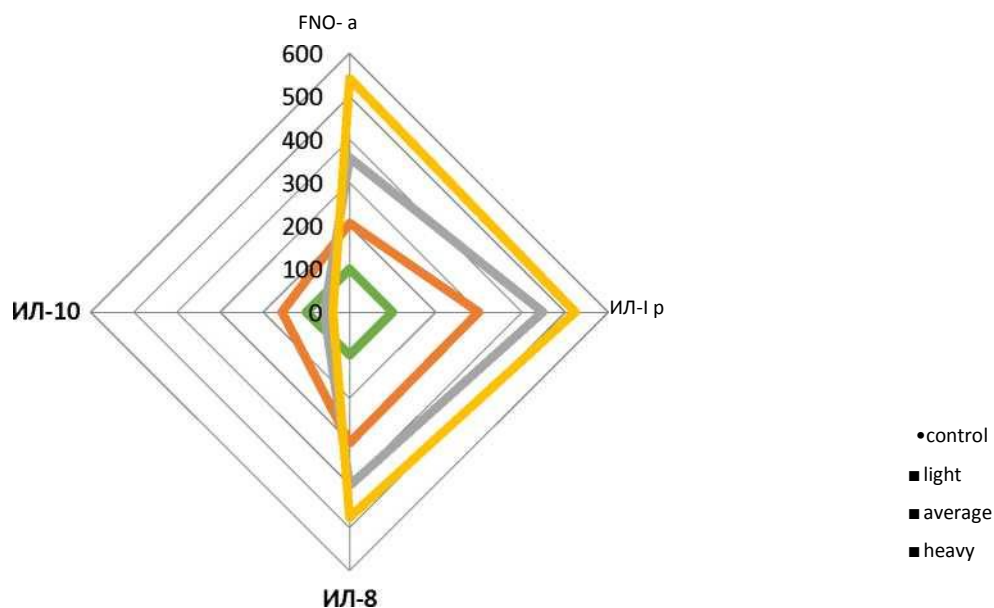
Indicators	Control	Patients with ASD, course of ASD		
		lung	average	heavy
<b>Mixed saliva</b>				
TNF-a ng/ml	10.02±0.50	20.62±0.99*	35.81±1.25* •	54.21±2.61* <sup>x</sup>
IL - 1B ng/ml	40.31±2.00	120.51±6.31*	180.42±9.00* •	210.88±10.03* <sup>^x</sup>
IL - 8 ng/ml	20.03±0.95	60.81±3.08*	80.61±3.64* •	95.31±4.25* <sup>x</sup>
IL-10 ng/ml	26.08±1.22	40.82±1.95*	15.31±0.72* •	10.25±0.48* <sup>x</sup>
<b>Serum</b>				
TNF-a ng/ml	1.42±0.07	2.01±0.10*	2.77±0.11* •	3.81±0.17* • <sup>x</sup>
IL - 1B ng/ml	7.05±0.32	11.25±0.52*	14.65±0.65* •	17.32±0.80* <sup>x</sup>
IL - 8 ng/ml	6.03±0.24	10.31±0.47*	12.24±0.59* •	15.31±0.65* <sup>x</sup>
IL-10 ng/ml	10.32±0.43	14.25±0.66*	6.32±0.24* •	4.31±0.20* <sup>^x</sup>

Note: \* - p<0.05 - in relation to the control;

• - p<0.05 - in relation to severe course;

<sup>x</sup> - p<0.05 - in relation to the course of moderate severity.

In our studies, the concentration of IL-ip increased progressively, more intensively in mixed saliva: in mild cases - by 198.96% (p<0.01); in the course of the disease of moderate severity - by 347.58% (p<0.01) and in severe course - by 425.15% (p<0.01); the corresponding dynamics in blood serum was 59.57% (p<0.01); 107.80% (p<0.01) and 145.67% (p<0.01) (table 1 and fig. 1)



**Mixed saliva**  
**Serum**

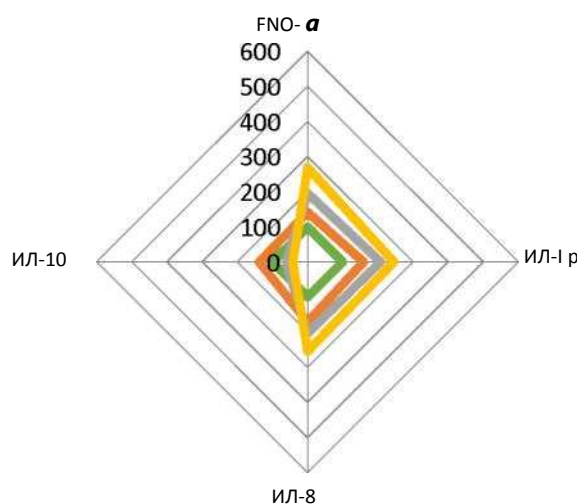


Figure.1. Dynamics of cytokine concentration in patients with ASD (in % in relation to the control - 100%).

TNF-a is an intense pro-inflammatory mediator and, as a result, edema. It is under the influence of TNF-a that the secretion of other pro-inflammatory mediators is stimulated and the number of leukocytes increases. Pro inflammatory cytokine IL-ip promotes production activated by the

endothelium of adhesion molecules, is the main indicator of local inflammation, and its accelerated formation leads to tissue destruction [24, 25, 26].

The biological function of the pro-inflammatory cytokine IL-6 is to regulate the active formation of B-

lymphocytes and immunoglobulins [25, 27].

The concentration of IL-6 in the oral fluid increased in mild ASD by 203.60% ( $p<0.01$ ); moderate - by 302.45% ( $p<0.01$ ) and in severe ASD - by 375.85% ( $p<0.001$ ). The activity of IL-6 expression in blood serum was somewhat lower and amounted to 70.98%, respectively ( $p<0.01$ ); 102.99% ( $p<0.01$ ) and 153.90% ( $p<0.001$ ) (Table 1 and Fig. 1).

IL-10 is the most important anti-inflammatory mediator, it helps to activate oral immunity, it increases the body's resistance and inhibits the expression of pro-inflammatory mediators [2, 24].

In patients with a mild course of ASD, in response to excessive production of pro-inflammatory cytokines, a compensatory increase in the anti-inflammatory cytokine IL-10 was observed, which amounted to 56.52% in mixed saliva ( $p<0.01$ ) and in blood serum - 38.07% ( $p<0.01$ ), which obviously provides a relatively favorable "mild" course of the disease.

An increase in the severity of the course is associated with a decrease in the cytokine balance towards the pro-inflammatory link, which is recorded by a decrease in the

concentration of IL-10. Thus, in the course of moderate severity, the concentration of IL-10 in saliva was increased by 41.30% ( $p<0.01$ ), and in blood serum - by 38.76% ( $p<0.01$ ); the corresponding reductions in severe cases were 60.70% ( $p<0.01$ ) and 58.24%.

Normally, the functioning of the mucosa is ensured by a balance between pro- and anti-inflammatory mediators. In patients with ASD at the systemic and local levels, an imbalance of pro- and anti-inflammatory mediators is recorded with a predominance of pro-inflammatory mediators, the overproduction of which contributes to the development and maintenance of erosive and ulcerative lesions of the oral mucosa.

The aggravation of the severity of the imbalance of pro- and anti-inflammatory cytokines with an increase in the severity of ASD indicates their pathogenetic role in the development of the disease.

Significantly higher concentrations of the studied about inflammatory markers in mixed saliva reflect the activity of local inflammation, and standardly high concentrations in blood serum reflect systemic disorders of the immune response

due to the severity of the background somatic pathology.

Cytokine profile in the dynamics of treatment. RAS is a chronic disease leading to the formation of a generalized immune response [1, 3]. The development of recurrent damage to C°PR associated with background somatic pathology of inflammatory genesis is invariably accompanied by an imbalance of Th1 and Th2 cytokines [4, 9, 10]. It is obvious that the consequence of the dynamics of the concentrations of pro- and anti-inflammatory mediators

makes it possible to evaluate the effectiveness of the treatment.

The results of the studies showed that before treatment in the compared groups, the same type of shifts in pro- and anti-inflammatory mediators were recorded, which made it possible to give a comparative assessment of the proposed treatment regimens (Table 2).

The concentration of cytokines in the comparison groups before and after treatment

Table 2

Indicator	A th Oh yu ~*~ b on koo et	Groups					
		1 comparison		2 main		3 main	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
<b>Mixed saliva</b>							
TNF-a	10.02±0.50	36.01 ±1.65	22.33* <sup>x</sup> ±1.01	36.25 ±1.65	17.66* <sup>xo</sup> ±0.81	35.98 ±1.62	10.62* <sup>o</sup> ±0.50
IL-1 p	40.31±2.0	181.25 ±9.11	70.21* <sup>x</sup> ±3.35	181.33 ±7.3	51.56* <sup>xo</sup> ±2.61	180.92 ±7.88	41.25* <sup>o</sup> ±2.03
IL-8	20.03±0.95	80.77 ±3.65	44.32* <sup>x</sup> ±2.04	81.02 ±8.35	31.5* <sup>xo</sup> ±1.62	80.95 ±3.51	22.31* <sup>o</sup> ±0.95
IL-10	26.08±1.22	15.44 ±0.71	20.32* <sup>x</sup> ±1.01	15.39 ±0.77	23.45* ±1.11	15.51 ±0.62	27.11* <sup>o</sup> ±1.22
<b>Serum</b>							
TNF-a	1.42±0.07	3.01 ±0.12	2.00* <sup>x</sup> ±0.09	2.99 ±0.13	1.72* <sup>x</sup> ±0.08	2.95 ±0.12	1.44* <sup>o</sup> ±0.04
IL-1 p	7.05±0.32	14.71 ±0.65	10.21* <sup>x</sup> ±0.45	14.66 ±0.66	8.50* <sup>xo</sup> ±0.40	14.77 ±0.65	7.20* <sup>o</sup> ±0.25
IL-8	6.03±0.24	12.31 ±0.59	9.25* <sup>x</sup> ±0.41	12.25 ±0.57	7.81* <sup>xo</sup> ±0.34	12.28 ±0.61	6.20* <sup>o</sup> ±0.18

IL-10	10.32±0.43	6.25 ±0.36	8.31* <sup>x</sup> ±0.37	6.27 ±0.29	9.00* <sup>x</sup> ±0.42	6.22 ±0.24	10.44* <sup>o</sup> ±0.47
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Note: x - p<0.05 in relation to the control group;

\* - p<0.05 in relation to the period before treatment; <sup>o</sup> - p<0.05 in relation to group 1;

L-p<0.05 in relation to the 2nd main group.

Analysis of the levels of the studied markers of intercellular interactions after treatment revealed their ambiguous dynamics.

In the group of patients who received antioxidant, sorption therapy and drugs aimed at restoring microbiocenosis in mixed saliva (main group 2), a decrease in the main pro-inflammatory cytokine TNF-a by 51.59% (p<0.01) was found below the values before treatment; at the same time, the concentrations of other anti-inflammatory mediators decreased IL-1 and IL-8 decreased relative to the values before treatment by 71.73% and 61.11% (p<0.01); the corresponding reductions in blood serum were 42.47% (p<0.01); 42.02% (p<0.01) and 36.24% (p<0.01).

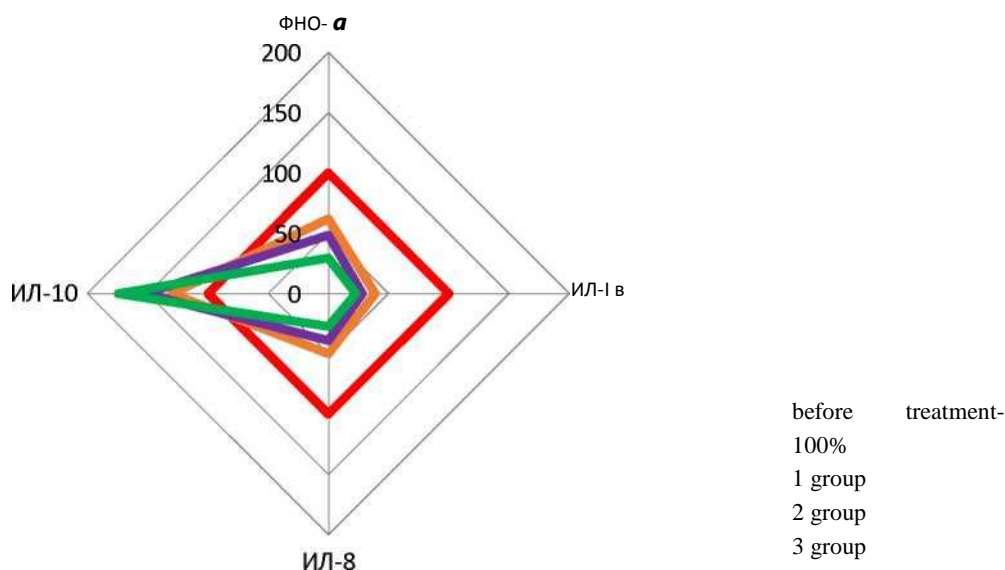
Against the background of a decrease in concentrations of pro-inflammatory mediators, an increase in the concentration of the main anti-inflammatory cytokine IL-10 was noted, equal to 52.34% (p<0.01) in mixed saliva and 43.54% (p<0.01) in blood serum (Table 2 ).

Thus, in the 2nd main group of patients, the enrichment of basic therapy with antioxidants and systemic sorbents and probiotics leads to a significant increase in the effectiveness of basic therapy.

At the same time, the inclusion of various antihistamines in the complex treatment leads to a decrease in pro- and an increase in anti-inflammatory cytokines to the level of the control group (healthy). At the same time, the level of TNF-a decreases relative to the value before treatment in mixed saliva by 70.48% (p<0.01); IL-1 c - by 72.20% and IL-8 - by 72.66% (p<0.01); accordingly, the dynamics in blood serum amounted to 51.19% (p<0.01); 52.25% (p<0.01) and 49.51% (p<0.01); increase the concentration of the anti-inflammatory cytokine IL-10 was 74.48% (p<0.01) in mixed saliva and 67.85% (p<0.01) in blood serum (Table 5.7, Fig. 5.4).



**Mixed saliva**



**Serum**

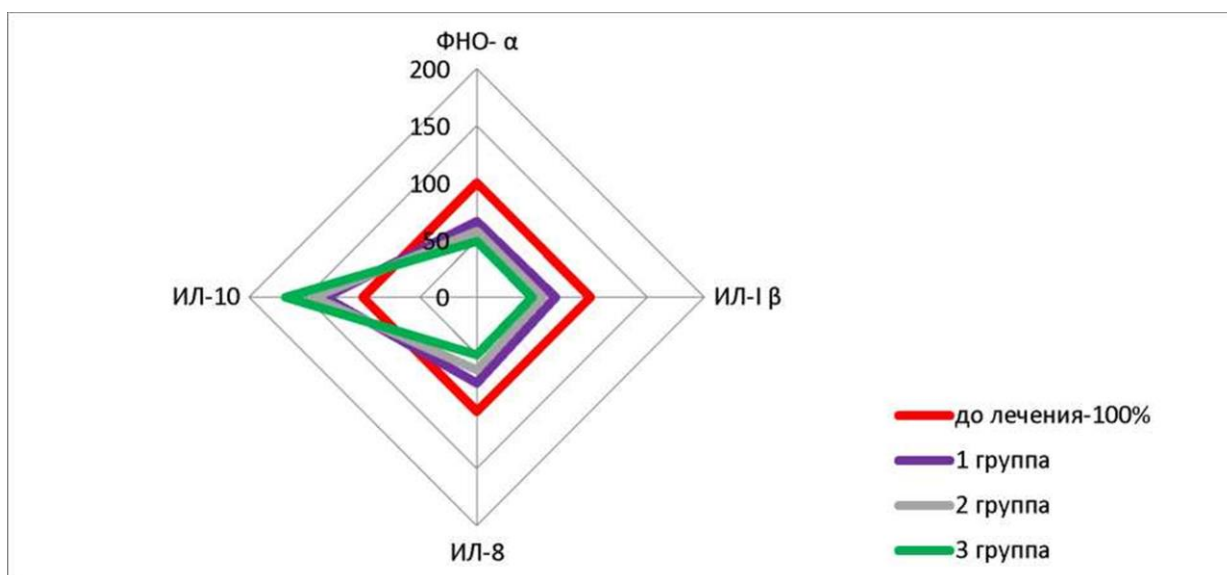


Fig.2. Comparative data on the dynamics of cytokines when using various methods of treatment in % in relation to size before treatment.

In this regard, not only the fact of the high efficiency of the developed methods of treatment, but also the extent to which their use increases the effectiveness of already used methods of treatment is of considerable interest.

A comparative analysis of the effectiveness of the developed treatment methods relative to the basic therapy is presented in Table 3.

Efficiency of treatment (in %) in comparison groups by dynamics.

Table 3

cytokine concentrations

Indicators	Comparis on group before	Main groups			
		2 main		3 main	
		K before treatment	K 1 group	K before treatment	K 1 1 group
<b>Mixed saliva</b>					
TNF-a	37.99	51.59	>14.17	70.48	>29.95
IL -l p	61.26	71.73	>7.87	77.20	>11.51
IL-8	50.07	61.11	>9.93	72.66	>18.41
IL-10	30.07	52.37	>27.05	74.48	>42.48
S, sum			59.02		102.35
M cf.			>14.76		>25.59
Place 3			2		1
<b>Serum</b>					
TNF-a	33.55	42.47	>11.73	51.19	>20.82
IL -l p	30.59	42.02	>15.74	51.25	>25.24
IL-8	24.86	36.24	>18.63	49.51	>29.22
IL-10	32.96	43.54	>13.83	67.85	>34.61
S, sum			58.93		109.85
M cf.			>14.98		>27.47
Place 3			2		1

As can be seen from Table 3, the effectiveness of treatment in the 2nd main group exceeds the 1st comparison group in mixed saliva in relation to the level of TNF-a> 14.17%; for IL-1p> 7.8%; for IL-8>9.93%; IL-10 >22.05%; similar dynamics in blood serum was >11.73%; >15.74%; >18.63%; 13.83%.

The comparative effectiveness of treatment in the 3rd main group was significantly higher and amounted to >29.95% in mixed saliva for TNF-a; for IL-1R> 11.51%; for IL-8>18.41%; IL-100 >42.48%; in blood serum respectively >20.82%; >25.24%; >29.22%; 34.61% (table 3).

At the same time, the average total efficiency in normalizing the cytokine



status in the 2nd main group exceeded the 1st comparison group in mixed saliva > 17.76%; in blood serum -> 14.98%; in the 3rd main group, respectively, >25.59% and >27.478% (Table 3).

Thus, the combination of antihistamines with methods that affect various mechanisms of the pathogenesis of the disease increases the effectiveness of basic therapy.

### CONCLUSIONS

In patients with ASD, at the height of the manifestations of the process in mixed saliva and blood serum, a progressive decrease in the levels of sIgA, IgM, IgA, an increase in the levels of sIgG, and also an increase in the concentration of pro-inflammatory cytokines TNF- $\alpha$ , IL-1 were registered. IL-8 and decreased anti-inflammatory marker IL-10. The association of the identified changes with the clinical severity of ASD indicates not only a decrease in the immune response of the body and the stability of the epithelium of the oral mucosa in a more severe course, but also the participation of an allergic component in the pathogenesis of the disease.

An analysis of clinical and biochemical parameters showed that the pathogenesis of the development of

severity of RAS at the local and systemic levels, along with an increase in proteolysis, pro-inflammatory cytokines and lipid peroxidation, significantly contributes to an increase in the content of the adhesion molecule, an increased level of histamine, and a decrease in the activity of diimine oxidase.

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