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CYTOKINE STATUS IN ADOLESCENTS WITH VARIOUS CLINICAL COURSES OF SALMONELLOSIS

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Abstract. *Salmonellosis in adolescents is a significant health concern, characterized by various clinical manifestations and influenced by factors such as age, comorbidities, and geographical location. Adolescents are particularly susceptible to both typhoidal and non-typhoidal Salmonella infections, which can lead to severe complications if not properly managed. The interaction between Salmonella and the host's immune response is complex, as Salmonella employs various virulence factors to evade immune detection and disrupt normal immune functions.* ***Purpose:*** *To evaluate the serum expression of pro-inflammatory and anti-inflammatory cytokines in adolescents with various clinical forms of salmonellosis and to determine their relationship with the inflammatory phase of the disease.* ***Methods:*** *Serum levels of IL-6, IL-8, IFN-γ, IL-17A, IL-10, and IL-13 were measured in adolescents with acute and prolonged salmonellosis, and compared with a control group. Cytokine concentrations were analyzed using descriptive statistics, median and interquartile range (IQR) calculations, and significance testing ($p<0.05$).* ***Results:*** *Adolescents with acute salmonellosis demonstrated marked increases in IL-6, IL-8, IFN-γ, and IL-17A, indicating activation of innate and Th1/Th17 immune responses. In the prolonged form, IFN-γ levels declined to control values, while IL-6 and IL-8 remained elevated, and IL-17A showed further increase, suggesting persistent Th17-driven inflammation. Anti-inflammatory cytokines IL-10 and IL-13 were elevated in both groups, with higher levels in the prolonged course, reflecting compensatory immune regulation.* ***Conclusion:*** *Cytokine profiling revealed distinct immune response patterns associated with different clinical forms of salmonellosis in adolescents. These findings highlight the potential utility of cytokine balance indices as biomarkers for disease activity and risk stratification, underscoring the relevance of cytokine monitoring in adolescent patients with salmonella infection.*

Keywords: *salmonellosis, adolescents, cytokine profile, IL-6, IL-8, IFN-γ, IL-17A, IL-10, IL-13, immune regulation.*

Introduction. Salmonellosis remains one of the most significant bacterial infections in childhood, and in adolescents, the disease is characterized by a wide range of clinical manifestations — from acute gastroenteritis to prolonged inflammation and chronic carriage [1, 4]. The outcome and clinical course of salmonellosis largely depend on the nature of the immune response, particularly on the balance between pro-inflammatory and regulatory cytokines, which reflects the integration of innate and adaptive defense mechanisms [6].

The analysis of immunological processes during adolescence is of particular importance, as this critical stage is accompanied by intense somatic, endocrine, and psycho-emotional changes. During this period — the so-called fifth critical stage of immune ontogenesis — the formation of the main adaptive subpopulations is completed, and mature immune regulatory circuits are established [14].

During puberty, sex hormones and cortisol exert a pronounced influence on immune function by modulating cytokine production, cytokine receptor expression, and the polarization of T-helper responses. During this period, there is a shift in the balance between the main pathways of the immune response (Th1, Th2, Th17, Treg), shaping individual characteristics of anti-infective defense [5, 2]. Depending on the type of infection, adolescents exhibit dominance of specific immune mechanisms: in bacterial infections — Th1/Th17 polarization, in viral infections — an interferon-mediated response, and in fungal infections — Th17 immunity [9, 3, 7].

Thus, adolescence is not only a period of profound endocrine and somatic restructuring but also a stage of final immune regulation maturation, which underscores the importance of studying cytokine profiles to better understand the mechanisms of immune response chronicity or dysregulation.

The aim of the study was to evaluate the characteristics of serum expression of pro- and anti-inflammatory cytokines in adolescents with different clinical courses of salmonellosis and to determine their relationship with the phase of the inflammatory process.

Materials and methods. Fifty-seven adolescent girls and boys participated in the study. Taking into account the clinical course of salmonellosis infection, the examined adolescents were divided into two main groups: the first group included 27 children with acute disease, and the second group included 30 adolescents with a protracted clinical variant. The control group consisted of 25 practically healthy adolescents of comparable age who had no signs of acute or chronic inflammatory processes.

The analysis did not reveal any significant differences in cytokine levels between boys and girls, so further analysis was conducted in a combined age group, which increased the statistical power and objectivity of the assessment of the cytokine response in adolescents.

Immunological studies in the examined patients were conducted at the Immunoregulation Laboratory of the Institute of Immunology and Human Genomics of the Academy of Sciences of Uzbekistan.

Serum concentrations of pro-inflammatory (IL-6, IL-8, IFN-γ, IL-17A) and anti-inflammatory (IL-10, IL-13) cytokines were determined by solid-phase enzyme-linked immunosorbent assay using test systems from Vector-Best and BioChemMac (Russia) in accordance with the manufacturer's recommendations.

Statistical data processing was performed using the Statistica 6.0 software package. Quantitative variables are presented as median (Me), interquartile range (Q1–Q3), and mean with standard error (M±m). The Student's t-test was used to assess differences between groups. Differences were considered statistically significant at $p<0.05$.

Results. Proinflammatory cytokines play a key role in initiating and regulating the immune response to bacterial infection, acting as the main mediators of acute inflammation, ensuring the activation of innate immune cells, stimulating the synthesis of acute phase proteins, and forming a local focus of inflammation for rapid elimination of the pathogen. In particular, IL-6 and IL-8 promote the mobilization and migration of neutrophils to the site of infection, enhance phagocytic activity, and maintain the local antimicrobial barrier. IFN-γ, as the main Th1-directed cytokine, activates macrophages and promotes the elimination of intracellular bacteria, while IL-17A, synthesized by Th17 cells, plays an important role in recruiting neutrophils and maintaining the integrity of mucous membranes. Balanced expression of proinflammatory cytokines is necessary for effective control of bacterial infection, but their excessive production can lead to the development of a hyperinflammatory response and tissue damage [4, 8, 12].

Table 1.

Serum levels of proinflammatory cytokines in the examined adolescents

Indicator	M±m, pg/ml	Me [Q1; Q3]	*p-value*
Control group, n=18			
IL-6	5,82±0,32	5,69 [4,68; 6,57]	-
IL-8	14,45±0,95	14,81 [9,71; 17,63]	
IFN-γ	23,11±1,26	21,36 [18,64; 25,84]	
IL-17A	10,05±0,63	9,74 [7,17; 13,47]	
Group 1 (severe course), n=22			
IL-6	34,89±2,19	35,41 [24,51; 45,72]	*<0,001**
IL-8	64,40±2,54	66,39 [54,02; 74,19]	*<0,001**
IFN-γ	44,39±2,00	41,73 [34,07; 51,84]	*<0,001**
IL-17A	21,54±1,09	21,36 [17,76; 25,33]	*<0,001**
Group 2 (prolonged course), n=28			
IL-6	17,43±1,15	17,97 [10,91; 21,35]	*<0,001**
IL-8	36,60±1,60	36,03 [29,48; 44,44]	*<0,001**
IFN-γ	18,16±0,81	17,74 [15,41; 19,74]	*>0,05^*
IL-17A	29,08±1,04	28,94 [27,57; 31,18]	*<0,001**

***Note:** * - statistically significant compared to the control group data. ^ - not statistically significant compared to the control group data. Median, Q1 (percentile) –25%, Q3 (percentile) – 75%.*

Interleukin-6 (IL-6) is a key pro-inflammatory cytokine involved in the initiation of acute inflammatory responses, activation of innate immune cells, and synthesis of acute-phase proteins [11].

According to the analysis of results, in the group with acute salmonellosis, the mean IL-6 level was 34.89 ± 2.19 pg/mL, which is six times higher than in the control group (5.82 ± 0.32 pg/mL). The median value was 35.41 pg/mL with an interquartile range of 24.51–45.72 pg/mL. This increase was statistically significant ($p < 0.001$), indicating high activity of the inflammatory cascade.

In the second group (prolonged course), the mean IL-6 level was 17.43 ± 1.15 pg/mL, which is nearly three times higher than the control but significantly lower than in the acute course.

Interleukin-8 (IL-8) is a chemokine that plays an important role in the recruitment and activation of neutrophils at the site of inflammation [1].

It was found that in the acute course group, the serum IL-8 level reached 64.40 ± 2.54 pg/mL, which is more than four times higher than the values in the control group (14.45 ± 0.95 pg/mL). The median level was 66.39 pg/mL, IQR: 54.02–74.19 pg/mL ($p < 0.001$).

In the prolonged course group, the IL-8 level was 36.60 ± 1.60 pg/mL (IQR: 29.48–44.44 pg/mL), which also significantly exceeded the control values ($p < 0.001$) but was lower than in the acute phase.

Interferon-gamma (IFN-γ) is the main cytokine of the Th1-cell response, activating macrophages and enhancing anti-infective defense against intracellular pathogens [12].

Data analysis showed that in the acute course group, IFN-γ reached 44.39 ± 2.00 pg/mL (1.9 times higher than the control — 23.11 ± 1.26 pg/mL; $p < 0.001$), with a median value of 41.73 pg/mL (IQR: 34.07–51.84).

In the prolonged course group, IFN-γ levels decreased to 18.16 ± 0.81 pg/mL, not differing significantly from the control values ($p > 0.05$), which may indicate attenuation of the Th1 response and insufficient pathogen elimination.

Interleukin-17A (IL-17A) is a key mediator of Th17 cells, inducing neutrophilic inflammation and enhancing mucosal defense [3].

In adolescents with acute salmonellosis, IL-17A levels were 21.54 ± 1.09 pg/mL, more than twice the control values (10.05 ± 0.63 pg/mL; p <0.001), with a median of 21.36 pg/mL (IQR: 17.76–25.33).

In the prolonged course group, IL-17A levels reached 29.08 ± 1.04 pg/mL (median: 28.94 pg/mL, IQR: 27.57–31.18; p <0.001), significantly exceeding both control and acute phase values.

The regulatory and anti-inflammatory immune response ensures the physiological resolution of inflammation, limiting systemic tissue damage and restoring immune homeostasis. During adolescence, the implementation of these mechanisms becomes particularly important due to the ongoing immunoendocrine adaptation characteristic of the final stage of immune ontogenesis. Against this background, anti-inflammatory cytokines—particularly IL-10 and IL-13—play key roles in controlling inflammatory activity by modulating the functions of antigen-presenting cells, reducing the expression of pro-inflammatory genes, and promoting the restoration of mucosal barrier integrity [10].

Table 2.

Serum Concentration of Anti-Inflammatory Interleukins in Adolescents with Salmonellosis

Indicator	M±m, pg/ml	Me [Q1; Q3]	*p-value*
Control group, n=18			
IL-10	2,25±0,19	2,41 [1,54; 2,59]	-
IL-13	4,58±0,18	4,71 [3,72; 5,35]	
Group 1 (severe course), n=22			
IL-10	6,61±0,47	5,82 [4,76; 8,60]	*<0,001**
IL-13	10,49±0,63	10,54 [7,02; 13,61]	*<0,001**
Group 2 (prolonged course), n=28			
IL-10	9,04±0,52	9,56 [6,87; 11,13]	*<0,001**
IL-13	7,91±0,48	7,85 [5,44; 10,51]	*<0,05**

***Note:** * – statistically significant compared to the control group. Me – median, Q1 (percentile) – 25%, Q3 (percentile) – 75%.*

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that plays a central role in the regulation of the immune response. It suppresses the synthesis of pro-inflammatory mediators (IL-1β, IL-6, TNF-α), reduces the expression of MHC II molecules and co-stimulatory receptors on antigen-presenting cells, and limits the activation of effector T lymphocytes [10].

Analysis of the results showed that in the acute disease group, the mean serum IL-10 level was 6.61 ± 0.47 pg/mL, which is 2.9 times higher than the control value (2.25 ± 0.19 pg/mL). The median value was 5.82 pg/mL, with an interquartile range of 4.76–8.60 pg/mL (p <0.001).

In the second group (prolonged course), the IL-10 level reached 9.04 ± 0.52 pg/mL (Me = 9.56 pg/mL; IQR: 6.87–11.13), which was statistically significantly higher than both the control values (p <0.001) and the levels in the acute course.

Interleukin-13 (IL-13) is a cytokine with regulatory and reparative functions, associated with the Th2-oriented immune response. It reduces the production of pro-inflammatory cytokines, promotes epithelial regeneration, and modulates fibrogenic processes [4, 14].

In adolescents with an acute course of the disease, the mean IL-13 level was 10.49 ± 0.63 pg/mL, which is more than 2.2 times higher than in the control group (4.58 ± 0.18 pg/mL). The median was 10.54 pg/mL, IQR: 7.02–13.61 (p <0.001).

In the prolonged course of the disease, IL-13 levels were 7.91 ± 0.48 pg/mL (Me = 7.85 pg/mL, IQR: 5.44–10.51), which was also statistically significantly higher than in the control ($p < 0.05$), but lower than in the acute course.

Discussion. The data obtained in the course of the study clearly demonstrate a pronounced imbalance between the pro-inflammatory and anti-inflammatory components of the immune response in adolescents with different clinical forms of salmonella infection. The observed dynamics of the cytokine profile reflect both the phase of the inflammatory process and the degree of involvement of the innate and adaptive arms of the immune system.

In the acute course of the disease, a significant increase in IL-6 and IL-8 levels was established, confirming active mobilization of innate immunity. IL-6, as a mediator of acute inflammation, and IL-8, acting as a neutrophil chemoattractant, create an effective inflammatory focus for rapid pathogen elimination. A substantial rise in IFN-γ indicates activation of the Th1-oriented cellular immune response, which is typical for defense against intracellular pathogens, including salmonella. At the same time, a moderate increase in IL-17A suggests additional activation of the Th17 axis, which supports neutrophilic inflammation and barrier protection. Taken together, these changes indicate the development of a full-fledged inflammatory response aimed at rapid clearance of the pathogen.

In the second group, characterized by a prolonged course of infection, a decrease in IL-6 and IL-8 levels compared to the acute phase was observed, which may be interpreted as a weakening of the inflammatory response against the background of ongoing pathogen persistence. The identified reduction in IFN-γ levels to values not significantly different from the control may indicate insufficient activity of the Th1 component and an inability of the immune system to achieve complete pathogen clearance. Paradoxically, the highest increase in IL-17A was observed in this group, which may reflect chronic activation of the Th17 axis under conditions of compensatory inflammation and disrupted mucosal immune homeostasis.

The anti-inflammatory mediators IL-10 and IL-13 showed a consistent increase in both clinical groups, with the highest values observed in the prolonged course. This may be interpreted as activation of compensatory mechanisms aimed at limiting tissue damage; however, excessive enhancement of regulatory signals may also contribute to reduced antimicrobial defense efficiency, particularly in the context of a diminished Th1 response

Thus, in acute salmonellosis, activation of innate and cellular immunity predominates, whereas in the prolonged course, an imbalance is observed with pronounced Th17 activation and dominance of immune regulation mediated by IL-10 and IL-13. This may explain the insufficient pathogen clearance and chronicity of the inflammatory process.

The presented data confirm that analysis of the cytokine profile, and particularly indices reflecting the balance between key cytokines, can serve not only as an indicator of inflammatory activity but also as a prognostic tool for stratifying patients according to the risk of a complicated course. These findings emphasize the relevance of incorporating cytokine status monitoring into the comprehensive immunological assessment of adolescent patients with salmonella infection.

Analysis of the cytokine profile in adolescents with salmonella infection revealed significant changes in the expression of pro-inflammatory (IL-6, IL-8, IFN-γ, IL-17A) and regulatory (IL-10, IL-13) cytokines depending on the clinical form of the disease. In the acute course, activation of innate and Th1/Th17 immune responses was observed, whereas in the prolonged course, there was an increase in regulatory activity along with persistent Th17 activation and a reduction in the Th1 component. These findings reflect the pathogenetic specificity of different forms of salmonellosis and highlight the role of age-related immune adaptation in shaping the clinical outcome of infection.

Conclusion.

1. Adolescents with acute salmonellosis are characterized by a significant increase in IL-6, IL-8, IFN-γ, and IL-17A levels, indicating activation of the systemic inflammatory response.

2. In the prolonged course of salmonellosis, IFN-γ levels do not differ significantly from the control, whereas IL-6 and IL-8 remain elevated, and IL-17A increases even further, suggesting a role of the Th17 response in maintaining persistent inflammation.

3. The increase in IL-10 and IL-13 concentrations in both forms of the disease reflects the activation of immunoregulatory mechanisms, which is particularly pronounced in the prolonged form.

4. Comparative analysis demonstrated that differences in cytokine profiles between clinical forms of salmonellosis can serve as immunological criteria for assessing the degree of inflammatory activity and the potential for chronicity, particularly in the adolescent population.

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