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THE ROLE OF CERTAIN CYTOKINES IN PREDICTING THE COURSE OF ACUTE SALMONELLOSIS IN CHILDREN

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ABSTRACT

Objective. This article investigates the role of cytokines in the pathogenesis of salmonellosis in children, depending on its clinical form (acute, prolonged, or chronic).

Materials and Methods. A total of 68 children aged 7–14 years, hospitalized at the RSNPMCEMP clinic with a bacteriologically and PCR-confirmed diagnosis of "Acute Salmonellosis," were examined.

Results and Discussion. In the acute form of the disease, a significant increase in pro-inflammatory cytokines IL-6 and IL-8 was observed, indicating a pronounced inflammatory response and activation of neutrophilic leukocytes. The timing and levels of these cytokines were closely correlated with the dynamics of inflammation and the clinical course of the disease. Elevated activity of regulatory cytokines, such as IL-10, was also detected, reflecting the engagement of immunoregulatory mechanisms to limit the inflammatory process. The article emphasizes the importance of the balance between pro-inflammatory and anti-inflammatory cytokines in determining clinical outcomes and the potential use of these markers to assess the severity of inflammation and predict the disease course in children with salmonellosis.

Keywords: Acute salmonellosis, cytokines, interleukins, inflammatory mediators.

INTRODUCTION

The infectious process represents one form of active interaction between a microorganism and its macroorganism host. Depending on the conditions of infection, the biological properties of the pathogen, and the state of the host's protective-adaptive systems, the infectious process may vary in severity. When an adequate immune response is mounted during the microorganism–host interaction, the infectious disease follows a cyclic course characterized by sequential developmental stages (incubation period, prodrome, period of main clinical manifestations, and convalescence). In cases of insufficient immune tension, an immunity incapable of eliminating the pathogen is formed, and the infectious process may take an acyclic course (recurrent, with exacerbations) (XXX).

The macroorganism exhibits a series of regularities in the response of protective forces to pathogen invasion and the development of inflammation at both local and systemic levels; these processes determine the clinical manifestations of the disease.

Salmonellosis remains one of the most common bacterial infections in childhood, characterized by wide variability in clinical manifestations—from classical acute gastroenteritic forms to prolonged courses with the development of chronic carriage. The outcome of the disease is largely determined by the nature of the cytokine response, which regulates the interaction between innate and adaptive immunity (1).

Upon infection with bacterial pathogens, cytokines play a key role in coordinating the inflammatory cascade, modulating the development and resolution of infection, determining the severity of clinical manifestations, and the likelihood of chronicity (2,3).

The immune response in school-aged children is characterized by specific features of inflammatory regulation, high plasticity of immune cells, and variability in the cytokine profile, associated with the stage of immune system maturation. The age range of 7–14 years corresponds to a period of relative immune stability; however, elements of cellular immaturity, a predominant humoral (Th2) response, and high sensitivity to antigenic stimuli remain characteristic of this age group (9).

The relevance of studying the immunological aspects of salmonellosis in school-aged children stems not only from the high prevalence of the disease but also from the significant frequency of transition to prolonged forms and the establishment of chronic carriage, which are closely linked to features of the cytokine profile. Despite considerable progress in investigating the immunopathogenesis of salmonellosis in children, the immunological characteristics of the cytokine response in school-aged children across different disease forms remain incompletely elucidated, underscoring the scientific and practical significance of the present study (1,3,10).

Based on the foregoing, the objective of this study was to examine the cytokine profile in children with acute salmonellosis exhibiting varying disease outcomes.

MATERIALS AND METHODS

In accordance with the stated objective, 68 children aged 7–14 years, hospitalized at the RSNPMCEMP clinic with a bacteriologically and PCR-confirmed diagnosis of “Acute Salmonellosis,” were examined. Depending on the clinical course of salmonellosis, patients were divided into two main groups: the first group comprised 22 children with an acute disease course, and the second group included 28 children with a prolonged course. The control group consisted of 18 practically healthy boys and girls of comparable age. Since analysis of the obtained immunological parameters revealed no significant differences between boys and girls, all examined children were combined into a single group for further analysis, ensuring representativeness and statistical reliability of the study.

Pro-inflammatory (IL-6 and IL-8) and anti-inflammatory (IL-10 and IL-13) cytokines were studied using immunological methods throughout the disease course.

RESULTS

Determination of serum IL-6 levels in the examined children revealed that in the first group (acute course of salmonellosis), the mean value of this cytokine was 26.68 ± 1.15 pg/mL, nearly 6-fold higher than the corresponding value in the control group (4.49 ± 0.39 pg/mL); the difference was statistically significant ($p < 0.001$). This pattern indicates massive activation of the innate immune response, typical of acute bacterial infections. Such a high IL-6 level likely

reflects not only active hepatic synthesis of acute-phase proteins but also systemic immune activation aimed at rapidly containing the infectious process.

In the second group (prolonged disease course), IL-6 concentration remained elevated, with a mean of 17.09 ± 1.28 pg/mL approximately 3.8-fold higher than control ($p < 0.001$) (Table 1). However, the elevation was less pronounced, possibly due to reduced inflammatory acuity amid prolonged antigenic stimulation and emerging deficiencies in pathogen elimination mechanisms, contributing to process chronicity.

Table 1. Serum levels of key pro-inflammatory cytokines in the examined children

Group	IL-6 (pg/mL) Mean ± SE	IL-8 (pg/mL) Mean ± SE
Acute (n=22)	26.68 ± 1.15*	52.67 ± 1.93*
Prolonged (n=28)	17.09 ± 1.28*	37.67 ± 1.53*
Control (n=18)	4.49 ± 0.39	11.75 ± 0.66

*Note: * – statistically significant compared to control.*

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine produced primarily by activated monocytes and macrophages, as well as endothelial cells, fibroblasts, adipocytes, and resident parenchymal cells in response to microbial components and damage signals. In the innate immune system, IL-6 initiates hepatic acute-phase protein synthesis, enhances B-cell differentiation into plasma cells and antibody class switching, stimulates adhesion molecule and chemokine expression, and—via STAT3—directs T-cell polarization toward the Th17 pathway while inhibiting Treg responses, thereby modulating the inflammation–regulation balance. In healthy children aged 7–14 years, basal IL-6 levels remain low due to resolution of postnatal innate hyperreactivity, whereas in vitro induced production increases owing to accumulated antigenic experience and activation of MyD88/STAT3 pathways (7,9).

Serum IL-8 in the first group (acute salmonellosis) also demonstrated significant and statistically reliable elevation compared to controls: mean 52.67 ± 1.93 pg/mL —more than 4.5-fold higher than in healthy children (11.75 ± 0.66 pg/mL; $p < 0.001$).

Such IL-8 values indicate intensive neutrophil migration and activation at the inflammatory focus, characteristic of the acute infectious phase (4,7).

In the second group (prolonged course), IL-8 was also significantly elevated versus control: mean 37.67 ± 1.53 pg/mL, approximately 3.2-fold higher than control ($p < 0.001$) but lower than in the acute phase. This pattern may reflect persistent but less intense neutrophil activation and inflammatory persistence, likely linked to unresolved antigenic load and prerequisites for chronic carriage (3,4).

Thus, analysis of IL-6 and IL-8 demonstrated that both cytokines serve as sensitive markers of bacterial inflammatory activity in school-aged children. In this age group, a propensity for enhanced humoral (Th2) response and relatively immature cellular immunity contributes to pronounced pro-inflammatory cytokine production during infection.

Interleukin-8 (IL-8, CXCL8) is synthesized by activated monocytes and macrophages, endothelial and epithelial cells, fibroblasts, and neutrophils themselves upon contact with

microbial products or pro-inflammatory stimuli. The primary function of IL-8 is chemoattraction and activation of neutrophils, ensuring their rapid extravasation, migration to the inflammatory focus, and release of antimicrobial enzyme-containing granules; additionally, IL-8 enhances angiogenesis and tissue remodeling, facilitating reparative processes. In healthy children aged 7–14 years, basal IL-8 is low due to absence of inflammatory stimulation; however, in vitro production exceeds that of early childhood, associated with accumulated antigenic experience and maturation of TLR/NF-κB signaling pathways (7,9,10).

The sharp rise in IL-6 and IL-8 during acute salmonellosis reflects intense innate immune activation and rapid engagement of effector cells for pathogen elimination. IL-6 stimulates acute-phase protein production and lymphocyte differentiation, while IL-8 ensures neutrophil migration and inflammatory focus formation.

Persistently moderately elevated IL-6 and IL-8 in prolonged courses indicate inadequate clearance and a tendency toward inflammatory persistence due to immaturity of certain immune mechanisms in this age category. This underscores the value of IL-6 and IL-8 as objective laboratory indicators of inflammation severity, infection activity, and chronicity risk in pediatric salmonellosis.

In the pathogenesis of infectious-inflammatory diseases, immune regulation—alongside pro-inflammatory reactions—plays a crucial role in controlling response intensity and preventing tissue damage. Anti-inflammatory and regulatory cytokines participate in inflammation resolution, homeostasis restoration, and tolerance development by modulating immune cell activity, suppressing pro-inflammatory mediator synthesis, and promoting regulatory T-cell expansion. Disruption of the pro-/anti-inflammatory signal balance may contribute to inflammation chronicity or reduced infection control efficacy. In children, immune response regulation features are linked to immune system maturation stages and manifest as variability in regulatory cytokine production and stimulation sensitivity. This underscores the relevance of studying the anti-inflammatory immune component in childhood infections for both pathogenetic understanding and optimization of prognosis and therapy.

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine whose primary function is to limit and terminate the inflammatory response. It is produced by a broad spectrum of cells, including regulatory T-lymphocytes (Treg), Th2 cells, B-lymphocytes, monocytes, macrophages, and dendritic cells, predominantly in response to microbial antigens and pro-inflammatory stimuli. IL-10 suppresses pro-inflammatory cytokine synthesis, reduces MHC II and costimulatory molecule expression on antigen-presenting cells, thereby limiting effector T-cell activation and preventing excessive inflammation. In children aged 7–14 years, basal IL-10 remains low, but the inducible response approaches adult patterns due to Treg maturation and immune experience (6,8).

Table 2. Serum concentrations of anti-inflammatory interleukins in children with salmonellosis

Group	IL-10 (pg/mL) Mean ± SE	IL-13 (pg/mL) Mean ± SE
Acute (n=22)	6.83 ± 0.49*	14.47 ± 1.13*
Prolonged (n=28)	10.21 ± 0.70*	10.24 ± 0.71*
Control (n=18)	2.51 ± 0.20	5.35 ± 0.54

*Note: * – statistically significant compared to control.*

Analysis of serum IL-10 in children with acute salmonellosis (Group 1) revealed a significant increase compared to controls. Mean IL-10 concentration was 6.83 ± 0.49 pg/mL. In the control group, mean IL-10 was 2.51 ± 0.20 pg/mL. Thus, IL-10 levels in acute disease increased approximately 2.7-fold versus control ($p < 0.001$).

Elevated serum IL-10 in acute salmonellosis likely reflects compensatory activation of immunoregulatory mechanisms aimed at limiting inflammation. IL-10 suppresses macrophage and antigen-presenting cell activity, reduces IL-1β, IL-6, and TNF-α production, and downregulates MHC II expression, thereby preventing tissue damage during hyperinflammatory responses (6,8).

In the prolonged-course group (Group 2), IL-10 elevation was even more pronounced: mean 10.21 ± 0.70 pg/mL, 4-fold higher than control ($p < 0.001$). This rise may reflect sustained anti-inflammatory pathway activation amid persistent antigenic load and pathogen persistence. Prolonged IL-10 synthesis stimulation in this clinical form likely restrains inflammation but may simultaneously weaken effector immune responses, creating prerequisites for infection chronicity and hindering complete focus sanitation (Table 2).

Interleukin-13 (IL-13) is a cytokine with predominantly regulatory and reparative functions, produced mainly by Th2 lymphocytes, as well as ILC2 cells, basophils, and eosinophils in response to antigenic stimulation or tissue damage. IL-13 promotes epithelial regeneration, mucus production regulation, suppression of pro-inflammatory cytokines and classical macrophage activity, thereby supporting homeostasis restoration post-inflammation (5).

In children aged 7–14 years, physiological IL-13 production remains low against a background of established Th1/Th2 balance, with preserved sensitivity of target epithelial cells due to active barrier tissue development.

Examination of serum IL-13 in Group 1 (acute salmonellosis) also revealed a statistically significant increase versus controls: mean 14.47 ± 1.13 pg/mL, median 14.47 [9.46; 20.01] pg/mL—2.7-fold higher than in controls (5.35 ± 0.54 pg/mL; median 4.82 [3.57; 7.59] pg/mL) ($p < 0.001$).

The increased production is likely associated with Th2-cell activation in response to intestinal mucosal damage and the need to stimulate epithelial repair. Moreover, its elevation in acute disease probably reflects an adaptive immune component aimed at limiting inflammation and maintaining tissue homeostasis.

In contrast to IL-10, IL-13 in prolonged disease was moderately elevated: mean 10.24 ± 0.71 pg/mL, 1.9-fold higher than control ($p < 0.001$) but significantly lower than in the acute form. This may indicate partial reduction in Th2-response activity during prolonged inflammation.

Possibly, under chronic antigenic stimulation, the regulatory effect of IL-13 becomes insufficient for effective inflammation control, or regulatory mechanisms shift toward other cytokine axes, including IL-10.

Thus, analysis of anti-inflammatory interleukins showed that both IL-10 and IL-13 significantly increase in childhood salmonellosis, reflecting activation of immunoregulatory mechanisms. However, in prolonged courses, further IL-10 elevation occurs alongside relative IL-13 reduction, likely indicating a shift in regulatory response character and potential dysfunction of inflammation-resolution mechanisms. The obtained data confirm the importance of assessing serum IL-10 and IL-13 as biomarkers of infection course and demonstrate their pathogenetic role in regulating the inflammatory process in salmonellosis.

CONCLUSIONS

1. Inflammation in childhood salmonellosis is accompanied by elevation of both pro-inflammatory and anti-inflammatory cytokines.
2. Levels of IL-6, IL-8, and IL-10 can serve as objective markers of infection activity and inflammation severity.

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