



## The pathogenetic role of some cytokines in the development and course of various clinical forms of urinary tract infections in children

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**Abstract. Background.** The purpose of the research: to study the content of interleukin-6 and interleukin-15 cytokines in the blood serum of children with urinary tract infection and to establish their pathogenetic role in the development of various clinical forms of the disease. **Materials and methods.** The study groups consisted of 84 children (mean age of  $10.0 \pm 1.3$  years). The main group was divided into subgroups: the first one — 17 children with acute pyelonephritis, the second — 21 patients with chronic pyelonephritis, the third — 16 children with acute cystitis, the fourth subgroup — 10 patients with unspecified urinary tract infections. The control group included 20 relatively healthy children. The content of interleukin-6 and interleukin-15 was evaluated by enzyme-linked immunosorbent assay. **Results.** It was established that the development of acute urinary tract infections was accompanied by a high level of serum pro-inflammatory interleukin-6. We found the highest level in children with cystitis, which exceeded that of the control group by 2.8 times ( $p < 0.01$ ). In children with acute pyelonephritis, this cytokine was 1.8 times higher ( $p < 0.05$ ). However, patients with chronic pyelonephritis had only a tendency towards its increase ( $p > 0.05$ ). Interleukin-15 in the main group was statistically higher than in controls ( $p < 0.05$ ). In children of subgroups 3 and 4, its level did not differ from that of the control group ( $p > 0.05$ ). However, in subgroups 1 ( $p < 0.05$ ) and 2 ( $p < 0.01$ ), we observed a statistically significant increase in interleukin-15 level. A direct correlation between interleukin-15 content and disease duration ( $r = 0.64$ ,  $p < 0.05$ ) was also found. **Conclusions.** The development of an acute inflammatory process in the urinary tract in children occurs against the background of a marked increase in the expression of interleukin-6, while a chronic inflammatory process develops with a statistically significant increase in the level of interleukin-15 in blood serum.

**Keywords:** children; infection of the urinary system; cytokines

### Introduction

Urinary tract infection (UTI) remains one of the most frequent reasons for visiting a pediatrician. The impact of inflammatory diseases of the urinary system on children's health is significant throughout childhood, from the newborn period to late adolescence [3]. UTIs are the second most common cause of antibiotic prescription in pediatric outpatients, second only to respiratory tract infections [23]. The diagnosis and effective treatment of urinary tract infections, despite their high prevalence, still pose significant challenges due to frequent occurrence, recurrences, and the rampant increase in antibiotic resistance worldwide [12]. Timely detection and adequate treatment of urinary system infections is the primary task of the doctor, because untreated

UTI and frequent recurrences in children can lead to persistent kidney damage (kidney scarring) and, over time, to the development of arterial hypertension, proteinuria, and chronic renal failure [22]. Therefore, it is necessary to understand the pathogenesis of UTI, as well as the body's defense mechanisms.

More and more data indicate a multifaceted role of the innate immune system in the development of UTI, including sanitation from uropathogens and prevention of a damage to the renal parenchyma and scarring [5]. It provides advanced protection against microbial damage and contributes to further activation of the adaptive immune system [19]. The innate immune system also includes local defense mechanisms, such as the bladder wall and uroepithelium,

which are of great importance in limiting the attachment and penetration of pathogens [11]. When various uropathogens violate the physical barriers of the urothelium, they are recognized by Toll-like receptors, which mobilize not only the immune responses of the epithelial cells of the urinary bladder and kidneys, but also induce a persistent urothelial cytokine response [19].

Cytokines are small (15–20 kDa) short-lived proteins that coordinate the development and activity of the immune system [16]. Interleukin-1 (IL-1), IL-6, and IL-8 are often the first cytokines detected in urine after infection. They are produced in response to bacterial infections and are important mediators of inflammation [1, 2]. IL-6 is a multifunctional cytokine that regulates numerous functions of the body, such as the acute phase response [2]. It is currently known that IL-6 stimulates the synthesis of acute phase proteins by the liver, promotes the proliferation and differentiation of B- and T-cells, and activates leukocytopoiesis. Macrophages, fibroblasts, vascular endothelium, T-cells and others have the ability to secrete IL-6 after their activation by pathogen-related molecules and some other factors.

IL-15 is a cytokine produced by various cells of the body, particularly renal epithelial cells, which acts on many cell types and connects the innate and adaptive immune systems [9, 15]. A characteristic feature of IL-15 is a certain structural and functional similarity with interleukin-2, but the specificity of IL-15 lies in the  $\alpha$ -chain of the receptor. IL-15 performs functions similar to IL-2: it stimulates the proliferation of activated T-cells, induces cytotoxic T-lymphocytes, generates, proliferates, and activates NK-cells [17, 24]. In contrast to interleukin-2, IL-15 has little effect on regulatory T-cells, while IL-2 inhibits T-cell response [4, 20, 24]. In addition to affecting T- and NK-cells, IL-15 influences other components of the immune system. Thus, IL-15 protects neutrophils from apoptosis, modulates phagocytosis, and stimulates IL-8 and IL-1R secretion. At the same time, increased activity of IL-15 can cause side effects associated with many human diseases, such as cancer, infections, and autoimmune inflammatory diseases [15]. Engelsöy U. et al. (2019) showed in their work that pro-inflammatory cytokines have the ability to change the virulence characteristics of uropathogenic *Escherichia coli* (*E.coli*), induce enhanced growth of the strain, which, in turn, can promote persistence in the urinary tract and cause UTI recurrences.

All of the above, together with the fact that studies of these cytokines in children with inflammatory processes in the urinary tract are sporadic and sometimes contradictory, served as a motive for conducting this study.

**The purpose:** to study the content of interleukin-6 and interleukin-15 cytokines in the blood serum of children with urinary tract infection and to establish their pathogenetic role in the development of various clinical forms of the disease.

## Materials and methods

We examined 84 children aged 6 to 14 years (the mean age was  $10.0 \pm 1.3$ ) who were hospitalized to the Zaporizhzhia Regional Children's Clinical Hospital during 2018–2020. The main study group included 64 children with primary uri-

nary tract infections. Patients with urinary tract abnormalities, as well as those who received antibacterial therapy prior to the experiment, were excluded from the study. The children were divided into groups taking into account the classification and criteria for the diagnosis of UTI, according to the 2021 European Association of Urology guidelines (levels of evidence I, II) [10] and the order of the Ministry of Health of Ukraine No. 627 dated 03.11.2008 [26].

The main group was divided into four subgroups: the first one included 17 children with acute pyelonephritis, the second — 21 patients with chronic pyelonephritis, the third — 16 children with acute cystitis, the fourth — 10 patients with unspecified urinary tract infections. The control group consisted of 20 relatively healthy children, representative by sex and age, without any signs of the urinary system inflammation.

The serum IL-6 and IL-15 concentrations were evaluated by enzyme-linked immunosorbent assay using Human IL-6 and Human IL-15 (Elabscience, USA) commercial kits, respectively.

The results obtained were processed by the method of variation statistics using statistical packages Excel and Statistica 13.0 (StatSoft Inc., No. JPZ8041382130ARCN10-J). The method of correlation analysis with the calculation of Spearman's rank correlation coefficient was applied. The non-parametric Mann-Whitney test (U) was used to assess differences between indicators. Differences were considered significant at  $p < 0.05$ .

All human studies complied with the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. A complete set of data on children, their parents and physicians confirming the results of this study was not publicly available due to limited initial ethics approvals.

## Results

The results of the research are shown in Table 1. As can be seen from its data, the development of the inflammatory process in the urinary tract was accompanied by a predicted statistically significant ( $p < 0.05$ ) increase in the level of IL-6 in the blood serum of children with UTI.

When working with the actual data, we paid attention to the high coefficient of variation in the main group ( $cV = 89\%$ ), which indicated its heterogeneity. Since patients with different levels of urinary tract damage participated in our study, we associated the high coefficient of variation of the indicator with this. Therefore, the next step of our work was to study the IL-6 content in children's blood serum taking into account the level of the lesion.

As can be seen from the data in Table 1, despite the presence of an increase in the IL-6 level in most subgroups, the degree of its expression was different. Thus, we found the highest level of IL-6, which exceeded that of controls by 2.8 times ( $p < 0.01$ ), in children of subgroup 3, i.e. patients with cystitis. Further ranking of the level of the specified cytokine showed that in patients with acute pyelonephritis, it exceeded the figures in the control group by 1.8 times ( $p < 0.05$ ). At the next step of the rank, there were children

**Table 1. The serum levels of IL-6 and IL-15 in the examined children, pg/ml**

Cytokine	Control group, n = 20	Study group, n = 64	Subgroup 1, n = 17	Subgroup 2, n = 21	Subgroup 3, n = 16	Subgroup 4, n = 10
IL-6	2.34 (1.9; 3.7)	3.4 (2.6; 6.4)*	4.2 (3.4; 6.9)*	2.8 (1.4; 5.2)	6.2 (4.4; 8.0)**	3.3 (2.4; 6.5)*
IL-15	0.22 (0.2; 0.23)	0.34 (0.22; 1.64)*	0.45 (0.3; 1.56)*	1.1 (0.22; 4.1)**	0.2 (0.2; 0.3)	0.22 (0.2; 0.4)

**Notes:** \*  $p < 0.05$  — compared with the control group; \*\*  $p < 0.01$  — compared with the control group.

from subgroup 4 in which the serum content of the studied pro-inflammatory cytokine exceeded the reference values by 1.41 times ( $p < 0.05$ ). The obtained data look quite logical, if we consider the fact that IL-6 is a pro-inflammatory cytokine that regulates the acute phase response, in particular, in the urinary system. At the same time, there was no reliable increase in the serum level of children of the second subgroup with chronic pyelonephritis, but only a tendency to its increase ( $p > 0.05$ ). The obtained data looked somewhat illogical, if we take into account that all children of this group were examined during the exacerbation period, that is, under activation of the inflammatory process. The explanation of this fact, obviously, lies in another plane of the development of the inflammatory process, with other ways of the course of low-grade chronic inflammation.

A different picture was observed when we studied the level of IL-15 in the blood serum of children who were included in the study. As can be seen from the data presented in Table 1, the level of IL-15 in the main group was statistically higher than that of the control group ( $p < 0.05$ ). In addition, the high coefficient of variation in the main group ( $cV = 84.6\%$ ) attracted attention, which emphasized the need to redistribute patients according to the level of damage and the specific course of the disease, as in the previous stage of the study. With this in mind, the next step of our work was to evaluate IL-15 in children of each selected subgroup. According to the data presented in Table 1, in patients of subgroups 3 and 4 with cystitis and unspecified UTI, IL-15 content did not differ from that in controls ( $p > 0.05$ ). However, in subgroups 1 ( $p < 0.05$ ) and 2 ( $p < 0.01$ ), we observed a statistically significant increase in the level of IL-15. The obtained data did not automatically repeat the picture obtained when the IL-6 content was investigated. Particular attention was paid to the results of subgroup 2, patients with chronic pyelonephritis, because the indicator was exceeded by more than 5 times, which emphasized the need for further analysis to interpret the obtained data. In addition, a direct correlation between IL-15 content and the duration of the disease ( $r = 0.64$ ,  $p < 0.05$ ) attracted attention.

## Discussion

We have demonstrated in our study that the development of acute urinary tract infections is expectedly accompanied by high levels of serum proinflammatory IL-6. The received data were confirmed in the work of Al Rushood M.A. et al. (2020) who also described an increase in the level of IL-6 in acute UTIs. Another researcher, Mazaheri M. (2021), also indicated a high content of IL-6 in acute inflammatory diseases of the urinary system; however, in this study, the level of serum IL-6 in children with acute pyelonephritis was higher than that in children with cystitis. Masajtis-

Zagajewska A., Nowicki M. (2017) in their review showed a diagnostically significant difference of IL-6 in the blood serum of patients with acute pyelonephritis and cystitis, resulting in suggestion that IL-6 could be used for differential diagnosis of upper and lower UTI. In our work, we obtained the opposite results: in cystitis, the level of serum IL-6 was significantly higher than in acute pyelonephritis, which indicates that studying this cytokine alone is not sufficient for differential diagnosis, and additional factors should be considered that require their further detection. In support of this assumption, the research of Al Rushood M.A. et al. (2020) showed that the difference between serum IL-6 in children with acute pyelonephritis and cystitis was not statistically significant. Therefore, we cannot confirm the hypothesis regarding the use of IL-6 as a biomarker for differential diagnosis of upper and lower UTIs. Ching B.C. et al. (2018) in their work demonstrated that uropathogenic *E.coli* strains suppress the secretion of IL-6 by urothelial cells, and a decrease in the amount of IL-6 leads to an increase in renal bacterial load and severe inflammation. Judging by these data, we can assume that the low level of serum IL-6 in children with chronic pyelonephritis may be due to a decrease in its secretion by uropathogens, and taking into account the data of Engelsöy U. et al. (2019) about the persistence of pathogens in the urinary tract, it could be suggested that this was one of the reasons for the chronicity of the process.

Peculiarities of IL-15 expression in children with urinary tract infections have not been studied enough to date. Thus, Devocelle A. et al. (2019) characterize IL-15 as a cytokine that acts as a potent survival factor and homeostatic factor for renal epithelial cells through autocrine loops, thereby protecting renal epithelial cells by counteracting apoptosis and inflammation is nephritis. Fiore P.F. et al. (2020) showed in their mouse study that under inflammatory and infectious conditions, the majority of circulating IL-15 is converted to a soluble complex isoform, acting as a rapid response to pathological conditions. The data of Ward P.A. (2007) who showed that excessive production of IL-15 improves the resistance of mice to infection with live *E.coli* look interesting. Thus, based on the above, as well as taking into account the results of our study, we can assume that one of the causes of elevated serum IL-15 level in children with chronic pyelonephritis was an increase in bacterial load.

At the same time, it was shown that regulation of the production of this interleukin occurs at several levels, mainly post-transcriptional, that is, at the level of protein translation and intracellular transport, unlike other cytokines, including IL-2. Therefore, if IL-15 production is not subject to translational control, its excessive expression occurs, which is accompanied by a violation of the homeostasis of the immune system with possible further chronicity of the process.

Indeed, studies have been described that determined the role of excessive synthesis of IL-15 in the development of inflammatory and autoimmune diseases by stimulating the production of tumor necrosis factor  $\alpha$ , IL-1P, as well as the activation of NK- and T-cells [14].

Thus, IL-15 becomes an active participant in the pathogenesis of bacterial diseases due to many immunoregulatory effects in its impaired production, disorders of regulation or signaling, and its role can be diametrically opposed, which requires further study and comparisons.

## Conclusions

1. The development of an acute inflammatory process in the urinary tract in children occurs against the background of a marked increase in the expression of the pro-inflammatory IL-6 in the blood serum, with the absence of statistically significant changes in this cytokine under chronic low-grade inflammation.

2. It was found that the development of a chronic inflammatory process in the urinary tract of children develops on the background of a statistically significant increase in the serum level of IL-15, with the absence of a reaction from IL-6.

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### Патогенетична роль деяких цитокінів у розвитку та перебігу різних клінічних форм інфекцій сечовидільної системи в дітей

**Резюме. Мета роботи.** Дослідити вміст цитокінів інтерлейкіну-6 та інтерлейкіну-15 у сироватці крові дітей з інфекцією сечовидільної системи та встановити їх патогенетичну роль у розвитку різних клінічних форм хвороби. **Матеріали та методи.** Групи дослідження становили 84 дитини (середній вік —  $10,0 \pm 1,3$  року). Основну групу розділили на підгрупи: 1-ша — 17 дітей, хворих на гострий пієлонефрит; 2-га — 21 пацієнт із хронічним пієлонефритом; 3-тя — 16 дітей, хворих на гострий цистит; 4-та — 10 пацієнтів із неуточненими інфекціями сечовидільної системи. Контрольну групу становили 20 умовно здорових дітей. Методом імуноферментного аналізу досліджено вміст інтерлейкіну-6 та інтерлейкіну-15. **Результати.** Установлено, що розвиток гострих інфекцій сечовидільних шляхів супроводжувався підвищенням рівня сироваткового прозапального інтерлейкіну-6. Найвищим він був у дітей, хворих на цистит, — у 2,8 раза більше за показники контрольної групи ( $p < 0,01$ ). У пацієнтів із гострим

пієлонефритом вміст цитокіну було перевищено в 1,8 раза ( $p < 0,05$ ). Однак у хворих на хронічний пієлонефрит ми спостерігали лише тенденцію до його зростання ( $p > 0,05$ ). Рівень інтерлейкіну-15 в основній групі був статистично вищим за показники контрольної групи ( $p < 0,05$ ). У дітей 3-ї та 4-ї підгруп його вміст не відрізнявся від такого в групі контролю ( $p > 0,05$ ). Проте в 1-й ( $p < 0,05$ ) та 2-й ( $p < 0,01$ ) підгрупах ми спостерігали статистично значуще підвищення рівня інтерлейкіну-15. Також встановлено наявність прямої кореляційної залежності вмісту інтерлейкіну-15 від тривалості захворювання ( $r = 0,64$ ,  $p < 0,05$ ). **Висновки.** Розвиток гострого запального процесу в сечовидільних шляхах у дітей відбувається на тлі вираженого зростання експресії інтерлейкіну-6, тоді як хронічний запальний процес перебігає із статистично значущим підвищенням рівня інтерлейкіну-15 у сироватці крові. **Ключові слова:** діти; інфекція сечовидільної системи; цитокіни