

COMPREHENSIVE IMMUNOMODULATORY TREATMENT IN CHILDREN WITH CHRONIC PYELONEPHRITIS*Sidikova Maryam Amangeldiyevna**Samarkand State Medical University, Republic of Uzbekistan, Samarkand.*

Annotation. *The purpose of the study.* To study the effect of immunomodulatory therapy on clinical parameters and the state of immunological reactivity in children with chronic pyelonephritis. **Material and methods.** 100 children aged 6-14 years with a recurrent course of chronic pyelonephritis (CP) were under observation. The first group of patients with CP (40 patients) received complex conventional therapy, the second group of patients with CP (30 patients) received complex treatment in combination with courses of polyoxidonium injections, the third group of patients with CP (30 patients) received complex treatment in combination with courses of injections imunofan. Clinical parameters were studied in patients, the content of populations and subpopulations of lymphocytes in the blood, immunoglobulins and circulating immune complexes in blood serum, phagocytosis parameters, and cytokine content in blood serum were studied in the active stage of the disease, the stages of partial and complete clinical and laboratory remission. **Results.** The first group of patients with CP who received complex conventional therapy experienced complete but short-term clinical and laboratory remission, during during which changes in many parameters of immunological reactivity were maintained. In the second and third groups of patients with CP who received complex treatment in combination with courses of injections of polyoxidonium and imunophan, the onset of prolonged complete clinical and laboratory remission was noted, during which normalization of immunological reactivity was recorded.

Key words: children, chronic pyelonephritis, immunological reactivity, immunomodulatory therapy, clinical and laboratory remission.

Introduction: Therapeutic measures for pyelonephritis in children are aimed at solving the following tasks: 1) elimination of the microbial-inflammatory process in the kidneys and urinary tract; 2) reduction of intoxication with high activity of the inflammatory process; 3) normalization of urodynamics in the urinary system; 4) normalization of immunological reactivity and stimulation of regenerative processes; 5) prevention of relapses of the disease. In the pathogenesis of pyelonephritis, an important role is assigned to immune disorders that accompany the course of the disease and affect the progression of the pathological process. In this regard, it is reasonable for patients to undergo courses of immunocorrective therapy, which helps to reduce the active period of pyelonephritis and reduces the risk of recurrence of the

disease [1, 12,14]. This paper presents the data obtained by us when we included in the complex therapy of children with chronic pyelonephritis courses of treatment with domestic immunomodulators of a new generation (polyoxidonium and imunophan) with anti-inflammatory, immunocorrective, membrane stabilizing and antioxidant effects.

The purpose of the study. To determine the effectiveness of including courses of treatment with new generation immunomodulators (polycosidonium and imunofan) in the complex therapy of children with chronic pyelonephritis. Research materials and methods. 100 children aged 6-14 years old with primary chronic pyelonephritis (CP) with preserved kidney function were under observation at the Kirov Regional Children's Clinical Hospital, which were divided into three groups depending on the therapy. The first group of patients with chronic pyelonephritis (40 patients) received complex conventional therapy: a diet with a slight restriction of protein and sodium chloride, the exclusion of spicy and salty dishes from the diet, mineral water "Nizhne-Ivinskaya" or "Borjomi" for 2 weeks, detoxification therapy, antibacterial therapy (amoxiclav in combination with cephalexin for 2 weeks, followed by the appointment of furagin in alternation with nitroxoline (for 2 weeks) for 6 months), drugs that eliminate secondary mitochondrial insufficiency (kudesan, riboflavin, L-carnitine, dimesphone), plant adaptogens (tincture of Eleutherococcus or ginseng root for 1 month). The second group of patients with chronic pyelonephritis (30 patients), along with the above-mentioned complex therapy, were prescribed polyoxidonium injections from the second day of hospital stay (at a dose of 0.1 mg / kg on water for injection, intramuscularly, two days later on the third, only 5 injections), and the third group of patients with chronic pyelonephritis (30 patients) – injections of imunofan (0.005% solution at the rate of 0.1 ml per year of life, but not more than 1.0 ml, subcutaneously, two days later on the third, only 5 injections). Repeated courses of injections of polyoxidonium and imunophan were prescribed to patients of the second and third groups 3 months after discharge from the hospital. They did not experience any complications or adverse reactions during treatment with polyoxidonium and imunophan. To assess the state of immunological reactivity in patients with chronic pyelonephritis in the first 1-2 days of follow-up (active stage of the disease), as well as in the stages of partial and complete. In laboratory remission, the content of populations and subpopulations of lymphocytes (CD3-1, CD4-1, CD8-1, CD20-1) in the blood, the content of immunoglobulins (Ig) G, A, M and circulating immune complexes (CIC) in serum were determined, indicators of phagocytic activity of neutrophils (FAN), phagocytic index (PHI) and the nitrosine tetrazolium reduction test (NST test) in the cytoplasm of neutrophils, the content of interferon-alpha (IFN- α), interleukin-1beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α) in blood serum. The results of these studies in patients with chronic pyelonephritis were compared with data obtained from 183 practically healthy children of the appropriate age living in Kirov and the Kirov

region of the Russian Federation. To determine the content of CD3-, CD4-, CD8- and CD20-lymphocytes in the blood of patients with chronic pyelonephritis, an indirect immunofluorescence reaction (RNIF) was used, where immunophenotyping is performed using sets of monoclonal antibodies LT3, LT4, LT8 and LT20, manufactured by Nizhny Novgorod NPC "Drug" LLC. The research results were expressed in percentages and absolute figures. The content of immunoglobulins of classes G, A, M in the blood serum of patients with chronic pyelonephritis was determined by enzyme immunoassay (ELISA) in accordance with the instructions for the Immunoscreen-G,A,M ELISA-Best reagent kit (Vector-Best CJSC, Novosibirsk); the results were expressed in g/L. The content of circulating immune complexes in the blood serum of patients with chronic pyelonephritis was determined by precipitation in a solution of polyethylene glycol.

The content of interferon-alpha, interleukin-1beta and tumor necrosis factor-alpha in serum in patients with chronic pyelonephritis was determined by enzyme immunoassay (ELISA) using reagent kits from Vector-Best CJSC (Novosibirsk); the results were expressed in pg/ml. The results obtained in the study of clinical and immunological parameters in patients with chronic pyelonephritis were processed by the method of variational statistics with the determination of the arithmetic mean (M), the mean square deviation (σ) and the mean square error (m), the coefficient of reliability of differences between the compared values (p) using the Student-Fisher table. The digital material was processed on a personal computer in the Microsoft Office Excel Mac 2011 application. The results of studies performed in groups of observed patients with chronic pyelonephritis were compared with each other and with the results of studies in practically healthy children of the control group.

Results and their discussion. In all observed children with chronic pyelonephritis, exacerbation of the microbial inflammatory process in the renal tissue was associated with acute respiratory disease. Upon admission to the hospital, they had clinical and laboratory signs of II-III degree of pyelonephritis activity. Patients complained of general weakness and malaise, increased fatigue, decreased appetite, headache, aching pain in the lumbar region, increasing at night time, frequent urination in small portions with the release of cloudy urine. On examination, all patients had pale skin and mucous membranes, 17% of patients had mild eyelid pasty in the morning, and 65% of patients had low nutrition. At admission to the hospital, 22% of patients had an increase in body temperature to 37.2-38 0C. In the active stage of the disease, tachycardia and muffled heart tones were noted in 80% of patients, an increase in blood pressure to 135/85 mmHg was detected in 11% of patients, and no significant changes were detected on the electrocardiogram. In all patients, there was a whitish-gray coating on the tongue, in 13% of patients the liver protruded from under the edge of the costal arch by 0.5-1 cm. All patients had pain during lumbar region shaking. In children with chronic pyelonephritis in the active stage of the disease, there was a

significant decrease in the number of red blood cells and a decrease in the level of hemoglobin in the blood, a decrease in color index, an increase in the total number of leukocytes, the absolute number of rod-shaped and segmented neutrophils, monocytes and eosinophils, a significant increase in ESR. Patients showed an acidic urine reaction, a significant increase in daily diuresis and a decrease in relative ISSN 2308-4804 were noted. Science and world. 2018. No. 11 (63). Vol. II. 50 urine density, small proteinuria, pronounced leukocyturia with a predominance of neutrophiluria, pronounced cylindruria (leukocyte, granular, hyaline cylinders in urine sediment), microhematuria, pathological bacteriuria (105-1012 microbial bodies in 1 ml of urine). In urine cultures, *Escherichia coli* was isolated in 77% of children with chronic pyelonephritis in the active stage of the disease, *Enterococcus* spp. in 10% of patients, *Staphylococcus* spp. in 5% of patients, and the microbial association *Escherichia coli* + *Staphylococcus* spp. in 8% of patients. In the active stage of the disease, patients showed a decrease in the level of total protein and albumins in blood serum, a decrease in the albumin/globulin index, and a significant decrease in glomerular filtration by endogenous creatinine clearance. Ultrasound examination of the observed patients with chronic pyelonephritis showed fragmentation of the pelvic echo signal, which is a sign of deformation of the cup-pelvic system, multiple small multi-amplitude echoes were recorded due to the presence of sclerotic changes in the parenchyma.

During excretory urography in patients with chronic pyelonephritis, asymmetry of damage to both kidneys was revealed in the form of a difference in the appearance of contrast medium in them, expansion of individual cups, the presence of deformed cups, asymmetry in the structure or size of cup cavities, contour interruption in the area of cups and necks of kidney cups. Renographic curves in patients with chronic pyelonephritis were characterized by a more gentle rise in the secretory phase, a late onset of excretion and a low rate of decrease in the excretory phase, asymmetry of secretory phase amplitudes on both sides, which is associated with varying degrees of damage to the right and left kidneys, an increase in the time to reach the peak of the renographic curve due to a violation of the tubular secretion process, as well as slowing down the excretion and outflow of urine from the kidney, associated with functional disorders of the urinary tract. In children with chronic pyelonephritis in the active stage of the disease, pronounced shifts in the parameters of immunological reactivity were noted (Table 1). Changes in the cellular link of immunity were manifested in patients in a decrease in the relative amount of CD3-1 ($p < 0.001$) with an increase in the absolute number of these cells ($p < 0.001$), a decrease in the relative amount of CD4-1 ($p < 0.001$) in the blood (Table 1), and the changes in the humoral link of immunity are in a decrease in the relative and absolute amount of CD20-1 ($p < 0.001$, $p < 0.001$) in the blood, a decrease in IgG ($p < 0.001$), an increase in IgM ($p < 0.001$) and CEC ($p < 0.001$) in blood serum (Table 1). However, in children with chronic pyelonephritis, the active stages of the disease (Table 1) showed signs of a decrease in nonspecific

antibacterial and antiviral resistance, manifested in a significant decrease in PHAN ($p<0.001$), PHI ($p<0.001$), HCT test ($p<0.001$), a decrease in IFN- ($p<0.001$) in blood serum, a pronounced increased content of proinflammatory cytokines (IL-1 and TNF-) in blood serum ($p<0,001$, $p<0,001$).

Table 1

Indicators of immunity and immunological reactivity in patients with CP (M m)

Indicators	Healthy children, n = 25	Patients with CP, active stage, n =100
CD3-L,%	54,20±0,64	47,67±2,12*
CD3-L,109/L	1,22±0,06	1,68±0,07*
CD4-L,%	48,20±1,34	38,11±1,77*
CD4-L,109/L	0,58±0,03	0,62±0,04
CD8-L,%	24,47±0,97	24,18±2,14
CD8-L,109/L	0,32±0,02	0,39±0,04
CD20-L,%	28,18±0,42	19,13±1,84*
CD20-L,109/L	0,65±0,02	0,37±0,02*
IgG,g/l	9,74±0,9	6,30±0,09*
IgA,g/l	1,12±0,07	1,17±0,07
IgM,g/l	1,18±0,04	1,67±0,04*

Note: "*" is $p<0.001$ compared to the indicators in practically healthy children.

Against the background of inpatient treatment, all observed children with chronic pyelonephritis showed a significant improvement in well-being, a decrease and disappearance of the main clinical symptoms of the disease. The length of stay of patients in the hospital was 13.4 0.4 days. When examining patients before discharge from the hospital, they were diagnosed with the onset of a stage of partial clinical laboratory remission, in which they did not complain, the general condition of the patients was satisfactory, no clinical symptoms, except for pallor of the skin and mucous membranes, were found in them, however, small shifts in clinical and laboratory parameters were noted. A month after discharge from the hospital, all observed children with chronic pyelonephritis had a stage of complete clinical and laboratory remission, during which

There were no clinical symptoms of the disease and normalization of clinical and laboratory parameters was noted. Studies have shown that in the first, second and third groups of patients with chronic pyelonephritis, ambiguous changes in the parameters of immunological reactivity were detected in the stages of partial and complete clinical and laboratory remission.

Table 2

The content of populations and subpopulations of lymphocytes in the blood, immunoglobulins and circulating immune complexes in serum in a group of patients with CP who received conventional therapy, in a group of patients with CP who received treatment in combination with polyoxidonium, and in a group of patients with CP who received treatment in combination with imunofan (M m)

Indicators	Healthy children, n = 25	Patients with Chronic pyelonephritis		
		the stage of complete clinical and laboratory remission		
		those who received conventional therapy, n=40	treated with polyoxidonium, n=30	treated with immunophane, n=30
CD3-L,%	54,20±0,64	50,75±1,59	55,28±1,32	57,05±1,42
CD3-L,109/L	1,22±0,06	1,24±0,04	1,24±0,07	1,27±0,11
CD4-L,%	48,20±1,34	42,71±1,56*	46,62±1,41	47,52±1,41
CD4-L,109/L	0,58±0,03	0,53±0,01	0,57±0,02	0,63±0,03
CD8-L,%	24,47±0,97	26,51±1,22	24,54±1,20	27,04±0,91
CD8-L,109/L	0,32±0,02	0,30±0,02	0,31±0,05	0,34±0,01
CD20-L,%	28,18±0,42	23,22±2,01*	28,42±1,51	26,32±1,51
CD20-L,109/L	0,65±0,02	0,62±0,04	0,69±0,05	0,70±0,07
IgG,g/l	9,74±0,9	7,14±0,10*	9,90±0,17	9,64±0,12
IgA,g/l	1,12±0,07	1,18±0,20	1,25±0,17	1,20±0,13
IgM,g/l	1,18±0,04	1,22±0,03	1,23±0,05	1,19±0,07

Note: "*" is $p < 0.001$ compared to the indicators in practically healthy children.

In the first group of patients with chronic pyelonephritis who received complex conventional therapy, at the stage of partial clinical and laboratory remission (Table 2), a decrease in the relative amount of CD3-L ($p < 0.001$) was noted with a slight increase in the absolute number of these cells ($p < 0.05$), a decrease in the relative amount of CD4-L ($p < 0.001$) and the relative amount of CD20-L ($p < 0.001$) in the blood.

At the stage of complete clinical and laboratory remission in the first group of patients with chronic pyelonephritis (Table 2), a relatively small decrease in the relative amount of CD4-1 ($p<0.02$) and the relative amount of CD20-1 ($p<0.05$) was detected in the absence of significant shifts in the content of other immunocompetent cells in the blood. In the second group of patients with chronic pyelonephritis who received complex treatment in combination with a course of polyoxidonium injections, in the stages of partial and complete clinical laboratory remission (Table 2), the content of populations and subpopulations of lymphocytes in the blood did not differ from the content of these cells in the blood of practically healthy children. In the third group of patients with chronic pyelonephritis who received complex treatment in combination with a course of imunofan injections, there were no significant changes in the content of populations and subpopulations of lymphocytes in the blood at the stage of partial clinical and laboratory remission (Table 2), and an increase in the relative amount of CD3-1 was noted at the stage of complete clinical and laboratory remission (Table 2) ($p<0.02$) in the absence of significant changes in the content of other immunocompetent cells in the blood. In the first group of patients with chronic pyelonephritis who received complex conventional therapy, at the stage of partial clinical and laboratory remission (Table 2), a decrease in IgG ($p<0.001$), an increase in IgM ($p<0.02$) and CEC ($p<0.001$) in serum was noted, and at the stage of complete clinical and laboratory remission (Table 2) – a decrease in IgG content ($p<0.001$) and a slight increase in the concentration of CEC ($p<0.05$) in blood serum. In the second group of patients with chronic pyelonephritis, who received complex treatment in combination with a course of polyoxidonium injections, in the stages of partial and complete after clinical and laboratory remission (Table 2), the content of IgG, IgA, IgM and CEC in blood serum did not differ significantly from these indicators in practically healthy children. In the third group of patients with chronic pyelonephritis, who received complex treatment in combination with a course of imunofan injections, there were also no significant changes in the content of IgG, IgA and IgM, and the concentration of CEC in blood serum in the stages of partial and complete clinical and laboratory remission.

Conclusion. In children with a recurrent course of primary chronic pyelonephritis with preserved renal function in the active stage of the disease, pronounced changes in the content of populations and subpopulations of lymphocytes in the blood, immunoglobulins and circulating immune complexes in the blood serum, phagocytosis and cytokine content in the blood serum are revealed. A group of patients with chronic pyelonephritis who received complex conventional therapy experienced complete but short-term clinical and laboratory remission, during which changes in the parameters of immunological reactivity persisted. The inclusion of two courses of injections of polyoxidonium and imunofan in the complex treatment of groups of patients with chronic pyelonephritis ensured the onset of prolonged complete clinical and laboratory

remission and normalization of immunological reactivity parameters. The results of clinical observations and special studies indicate high clinical, immunomodulatory and anti-relapse effects of complex treatment in combination with courses of injections of polyoxidonium and imunophan in children with chronic pyelonephritis.

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