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# IMMUNOLOGIC CHARACTERIZATION OF PECULIARITIES OF PROGNOSIS AND PROPHYLAXIS OF PURULENT-SEPTIC COMPLICATIONS OF LIVER ECHINOCOCCOSIS

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**Abstract**
The application of the developed therapeutic and diagnostic algorithms allowed, in the main group of patients in comparison with the control group, to increase the number of good treatment results from 30.9% to 35.1%, satisfactory - from 53.4% to 56.4% and to reduce unsatisfactory treatment results from 14.8% to 8.1%, and lethality - from 1.0% to 0.3%.

**Keywords** Echinococcosis of the liver, therapeutic and diagnostic algorithms, gisurgical treatment.

## INTRODUCTION

Echinococcosis of the liver is a severe parasitic disease caused by a tapeworm belonging to the genus Echinococcus (E. granulosus). The disease is most common in regions where livestock farming is popular. The region of Central Asia is in one of the zones characterized by endemic pathology of liver echinococcosis. However, in recent years, more and more information has been published regarding the prevalence of this disease in regions, particularly in Europe, where previously

echinococcosis of the liver was considered a sporadic case (1,3,5,7,9,11,30). The incidence of echinococcosis of internal organs, due to the peculiarities of pathomorphological manifestations of the disease, in the form of organization of specific cysts prone to dissemination, is considered to be very costly for the social sphere. Given that this disease most often affects people of working age, the pathology is reflected in the increase in the number of disability, and in the absence of treatment - in the increase in mortality (2,4,6,8,10,10,12,31).

According to the World Health Organization, diagnosis and detection of the hydatidiform form of liver echinococcosis should be considered a neglected form of the disease. However, at the same time, in half of cases of morbidity, due to the vague clinical picture, more dangerous is the development of complications of the disease, in particular - purulent-septic (13,15,17,19,32).

The spectrum of the disease depends on the acquired abnormality of Th1-associated immunity, and spontaneous secretion of IL-10 by peripheral blood mononuclear cells has been identified as an immunologic feature of patients with advanced forms of hepatic echinococcosis involved in the maintenance of tolerance and persistence of the parasite (14,16,18,20). Reactivity of peripheral blood cells to ribbon parasite antigens persists for many years in patients after complete resection of parasitic lesions, suggesting that residual parasite tissue will continue to stimulate cellular responses (21,23,25,27,29).

However, all of the above is only speculation based on findings on the pathogenesis of other parasitic diseases. At the same time, revealing the possibility of stimulating the immunologic response of the organism to the invasion of the echinococcal parasite would, in our opinion, allow us to develop methods of prediction and prevention of severe complicated forms of the disease, and, accordingly, to improve the results of treatment of patients with hydatidosis echinococcosis of the liver.

In this regard, the aim of our study was to improve the results of treatment of patients with hepatic echinococcosis by determining the role and place of immunopathogenetic aspects in the prediction and prevention of purulent-septic complications in this disease.

Material and methods of research. The work consists of clinical and experimental parts. Clinical material consists of 594 patients with hydatidosis echinococcosis of the liver (control - 298 patients and main - 296 patients), who were treated and examined in Bukhara regional multidisciplinary clinic from 2010 to 2023. Experimental studies were conducted on pedigree-free rabbits, which were in the vivarium of the central research laboratory of the Bukhara State Medical Institute. A total of 45 animals weighing 1.5-2.0 kilograms, both sexes, without external signs of disease were used.

Patients meeting the following criteria were included in the study: Patient's written consent to the study, patient's age should not be younger than 18 years and not older than 75 years, patients who met the following criteria were excluded from the study: presence of severe concomitant (somatic) disease in the acute phase of its development, patient's age younger than 18 years or older than 75 years.

The division of patients by sex and age revealed the predominance of the female sex (60.6%) at the age of 51 to 60 years. Patients with primary hydatidosis echinococcosis of the liver were predominant (72.1%). The second place was occupied by patients with recurrent hydatidosis echinococcosis of the liver, among which patients with multiple forms prevailed, exceeding solitary formations 1.5 times. In 71 cases (12.0%) the residual forms of hydatidosis echinococcosis of the liver were diagnosed, which occurred in almost the same proportion as solitary and multiple forms. The difference between them was 1.2 times in favor of multiple parasitic liver cysts. In 36.1% of cases the parasite in hydatid liver cysts was alive, and in 27.6% of cases it was dead. Complicated forms of the disease (cyst suppuration; suppuration of hydatidosis echinococcosis of the liver, with breakthrough into intrahepatic bile ducts, with development of cholangitis and mechanical

jaundice; suppuration of parasitic cyst with breakthrough into pleural cavity, with subsequent development of pleural empyema; suppuration of parasitic cyst of the liver, with breakthrough into the pleural cavity and further into the bronchial tree, with the development of purulent endobronchitis; perforation of echinococcal cyst of the liver into the free abdominal cavity with the development of peritonitis) were in 36.3% of cases.

To achieve the desired goal, the total array of experimental studies was divided by us into 3 series of experiments: Control series - consisted of 10 intact animals, which were not subjected to any external influences except for blood sampling. Main series - consisted of 10 animals and was subdivided by us into 3 components, which determined the chronology of modeling the pathological process. As necessary (death, incorrect manipulation, lack of model reproducibility, etc.). the series was supplemented with new animals. The main series of animals in the thesis work was denoted by three values as main-1, main-2 and main-3, which was conducted conditionally due to the transformation of the pathological process in the dynamics of its development. The process of modeling pathological processes was composed of several chronologically progressing stages. At the first stage, the main goal was modeling of hydatidosis echinococcosis of the liver. For this purpose, the animals were sedated using ether anesthesia. An oblique incision in the right subcostal region up to 5 cm long was made. Exposing the animal's liver, a position was created to maximally pull the organ distally. The diaphragmatic surface of the liver was visually evaluated, preserving all ligamentous elements of the organ. With the length up to 1.0 cm and depth up to 0.5 cm, the tissue of the organ on its diaphragmatic surface was dissected by electrocoagulation to form a well-shaped defect with the dimensions of 0.5x0.5 cm. Having removed the liver flap, the wound surface was thoroughly coagulated, achieving complete hemostasis and cholestasis. The daughter bubble of the echinococcal cyst was lowered into the formed cavity. Slaughtering of the animal was mandatory in case of lethal outcome in the course of the ongoing study or at the onset of the scheduled date of morphological studies.

Clinical, immunologic, biochemical, morphologic, ultrasound, radiologic, analytical and static research methods performed in the Central Research Laboratory of Ibn Sina Bukhara State Medical Institute were used.

All research methods were divided into standard and special (immunologic). Skin allergy test by Katsoni method, latex agglutination reaction, indirect hemagglutination, immunoenzyme analysis method, general blood tests, biochemical blood tests (total protein and its fractions - albumin and globulin with their division into subfractions; total bilirubin and its direct fraction; AsAt and AlAt activity, thymol test, urea and creatinine), inflammatory markers (C-reactive protein and procalcitonin, leukocyte intoxication index), ultrasonic diagnostics, multispiral computed tomography, magnetic resonance tomography.

In patients of the control group special or immunologic methods of research included determination of lymphocytes in peripheral blood, content of T-lymphocytes and their subpopulation composition of T-helper/inducers (CD4+ T-lymphocytes) T-suppressors/killers (CD8+ T-lymphocytes), serum immunoglobulins IgA, IgM, IgG, circulating immune complexes. In patients of the main group and in experimental animals the study of the immunologic status of the organism was carried out in a more extended variant. In the patients of the main group the same technique of blood sampling was carried out in terms of the first treatment of patients in the clinic and further on 14, 30, 60 days, as well as in 6 months and 1 year, which was associated with the assessment of the long-term results of treatment. In order to compare the prognostic efficiency and sensitivity of the testing methods developed by us, 10 volunteers from among healthy persons recognized as such by the medical commission were voluntarily involved in the research. The scope of the studies included: quantification of cytokine secretion in pg/mL (IL-8, IL-9, IL-10, IFN-γ, IL-12 and TNF-α) and chemokines in pg/mL (CCL13, CCL17, CCL18, CCL20, CCL22); quantitative determination of cellular immunity indicators (CD4+ CD28+, CD8+

CD28+, CD4+ CD25+); determination of IgG, IgG4, T-IgE and S-IgE immunoglobulin concentrations. To evaluate the immediate treatment results of patients with hydatidosis echinococcosis of the liver both in the control and main groups, we used our improved grading scale consisting of the criteria of the presence and nature of surgery, residual cavity in the liver, general and local postoperative complications. To study the distant results of treatment and quality of life of patients with hydatidosis echinococcosis of the liver both in the control and in the main groups we used our improved grading scale consisting of the criteria of presence and character of the residual cavity in the liver, the outcome of the disease, prognosis, work capacity at present, life activity, perception of own health, assessment of the quality of life and relationships in the family.

## RESULTS

The analysis of the results of traditional methods of treatment in 298 patients with hydatidosis echinococcosis of the liver showed that the primary forms of liver echinococcosis prevailed (75.8%) according to the nature of the disease, to a lesser extent - with recurrent (15.4%) and residual (8.7%). Solitary forms of hepatic echinococcosis (61.1%) prevailed over multiple forms (38.9%). In 49% of cases there was a complication of hepatic echinococcosis in the form of cyst suppuration (53,4%), cyst suppuration with breakthrough into intrahepatic bile ducts with the development of cholangitis and jaundice (37%), Echinococcal cyst suppuration with rupture into pleural cavity and development of pleural empyema (6,2%), cyst rupture into free abdominal cavity with development of peritonitis (2,1%), cyst suppuration with rupture into bronchial tree (1,4%). Open echinococcectomy was performed in 80.9% of cases. The predominant method of eliminating the residual liver cavity by capitonage with external drainage (62.2%). The following complications were noted in the postoperative period: wound suppuration (8.4%), exudative pleuritis (7.7%), acute bronchopneumonia (5.7%), pleural empyema (5%), wound ligature fistula development (4.7%), biliary fistula formation (4.4%), residual liver cavity abscess (3.7%), wound infiltrate (3.4%), sepsis (3.4%), seroma formation (3%), acute urinary retention (2.3%), marginal wound necrosis and euteration of internal organs (2%), rib osteomyelitis (1.7%), peritonitis (1.7%), liver failure (1.7%), subcutaneous hematoma (1.3%), myocardial infarction (1%), intra-abdominal hemorrhage (0.7%), acute cerebral circulatory failure (0.7%), acute renal failure (0.7%).

In 3-12 months after surgery, complete reduction of residual liver cavity was noted in 78.5%-95.6% of patients. During this period 6 more patients (2%) died. Disease recurrence was diagnosed in 10.4% of cases, and the presence of residual cysts - in 7.4% of cases.

When evaluating the structure of postoperative complications, we revealed the predominance of the frequency of negative consequences of inflammatory and disseminating nature. A certain role in this is played by the change in the general reaction of the organism. Thus proceeding from the materials of literature, reflecting the violation of immunological system of an organism in pathogenesis of echinococcosis occurrence, connected with sensitization of an organism and organization of rejection reaction it is possible to assume about presence, certain gap of researches in the given field of medicine.

We have proved that negative results of treatment, both in the immediate and in the distant period after liver echinococcectomy, are often associated with the lack of a way to assess immunologic changes. The study of clinical and laboratory, biochemical and primary immunologic manifestations, changes of inflammatory markers in patients with liver echinococcosis showed that the average number of CD8+ T-killer cells in all patients of the control group amounted to 621,92±231,16 cells in 1 µl of blood. The maximum number was observed among patients with recurrent form of the disease (713,27±186,82 cells in 1 µl of blood), and the minimum number was observed among patients with primary echinococcosis of the liver (516,84±103,17 cells in 1 µl of blood). The number of CD8+ T-killer cells in

the comparative analysis in patients with living echinococcosis averaged 522,32±116,52 cells in 1 µl of blood, with dead - 628,97±219,65 cells in 1 µl of blood, and with complicated - 714,48±276,33 cells in 1 µl of blood. At that, if in patients with dead echinococcus the number of CD8+ T-killer cells increased in comparison with patients with live parasite by 106,65±45,53 cells in 1 µl of blood, in patients with complicated form of the disease the increase was already by 192,16±36,14 cells in 1 µl of blood. The smallest difference in the increase in the number of CD8+ T-killer cells was between dead and complicated parasites (85,51±25,33 cells in 1 µl of blood). The comparison of the increase in the number of CD8+ T-killer cells in patients with complicated forms of liver echinococcosis compared to uncomplicated ones was 2.25 times ($p<0.05$). Comparison of the number of CD8+ T-killer cells between patients with living and dead parasite showed that the maximum level of difference was revealed in its residual forms (166,38±41,74 cells in 1 µl of blood). At the same time, in patients with complicated forms of liver echinococcosis, when comparing with the total number of cases with live and dead parasite, the maximum increase in the number of cells was observed in patients with relapsed form of the disease (623,96±211,53 cells in 1 µl of blood).

The given data can directly testify to the development of T-killer role activity as inflammatory or other kind of complication of liver echinococcosis develops. At the same time, the level of T-helpers changes in the opposite direction, combining by the nature of lesions of clinical cases with live and dead parasite, but without complication, especially of inflammatory nature. The maximum amount of IgA in blood was revealed by us among patients with complicated forms of liver echinococcosis (2.94 times; $p<0.05$). At the same time, the peak of this value occurred in patients with recurrent complicated form of liver echinococcosis (3.14-fold increase; $p<0.05$). The mean amount of IgM content was almost identical to the previous immunoglobulin. Despite the relative lower mean of IgM than IgA, there was an overall comparative increase in patients with recurrent hepatic echinococcosis. At that, high titer of IgM in patients with recurrent forms of hepatic echinococcosis (3.23 times; $p<0.05$), was due to the duration and recurrent development of the disease. There was an increased difference of IgM content in patients with hepatic echinococcosis depending on the viability of the parasite. In particular, in patients with dead parasite, IgM titer in blood increased by 0.28±0.1 g/L ($p<0.05$). The average level of IgG in patients with hepatic echinococcosis was 13.01±2.35 g/l. The maximum peak of this immunoglobulin titer was in patients with recurrent forms of the disease (15,71±3,11 g/l), and the minimum - in patients with primary hepatic echinococcosis (9,15±1,08 g/l; $p<0,05$). Depending on the form of the disease, we can note the average high titer of IgG in blood in patients with complicated forms of liver echinococcosis (14,6±3,52 g/l; $p<0,05$) and with a live parasite without complication of the pathologic process (13,41±2,72 g/l; $p<0,05$). In case of dead parasite, the level of IgG titer was at an intermediate level and averaged 11.03±3.12 g/l ($p<0.05$). The study of circulating immune complexes in blood in patients with hepatic echinococcosis amounted to 117.35±39.12 optical units. On average in patients with primary hepatic echinococcosis it amounted to 97.69±25.62 optical units, in the residual form - 119.17±27.13 optical units, and in the relapsed form - 135.19±23.43 optical units. These data confirm the cumulative character of circulating immune complexes. The increase in blood concentration of circulating immune complexes was observed in all patients with relapsed form of the disease. At the same time, the minimum level occurred in patients with live parasite, and the maximum - in patients with complicated form of the disease (increase in 1.99 times). The comparative difference between patients with uncomplicated and complicated forms of the disease showed an increase in favor of complicated forms of the pathological process (an increase of 144.56±41.45 optical units; $p<0.05$). The mean difference in this category was 83.96±21.76 optical units ($p<0.05$).

Thus, evaluation of initial value of laboratory parameters in patients with liver echinococcosis can testify to their differentiated value first of all

among patients with complicated and uncomplicated forms of the disease. It is also necessary to cancel separately reliable changes of biochemical indices characterizing liver disorder connected with disturbance of both bile formation (hepatic jaundice) and its passage (mechanical jaundice). The comparative analysis of CD4+/CD8+ cells ratio in blood in patients with different forms of liver echinococcosis showed that the maximum difference (in the order of 1.37 times) was noted by us in patients with primary liver echinococcosis, while the minimum one - in patients with recurrent one (1.06 times). That is, the increase in the number of T-helpers in patients with relapsed form of liver echinococcosis was accompanied by the cumulation of T-killers (r=0,729). The similar character of changes in the studied T-lymphocytes was also noted by us among patients with complicated form of the disease (0.84 times). The inverse correlation difference (r=-0,611) in the changes in the number of T-lymphocytes subpopulations was observed in patients with living liver echinococcosis (1,54 times). The difference in the number of T-lymphocytes subpopulations between patients with living and dead liver echinococcosis was insignificant.

We stated the increase of sensitization in patients with recurrent complicated form of liver echinococcosis. However, if in case of comparison of IgG level in blood between patients with live and dead parasite we can determine the difference in decrease of IgG titer by 9,06±2,43 g/l (p<0,05) in patients with dead primary parasite, then in cases with residual and with relapsed form of the disease there was no significant decrease of titer. This is what led to low differential significance of IgG between patients with live and dead uncomplicated hepatic echinococcosis. In patients with primary hepatic echinococcosis, the significance of IgG growth is essential in the diagnosis of the disease. The study of the peculiarities of changes in cellular and humoral immunity in different experimental models of liver echinococcosis showed that already on the 20th day of the study the number of CD4+CD28+ T-cells sharply increased among the animals with the main series of experiments from 27,49±1,12% to 46,93±3,91% (p<0,05). At the same time, the level of cells in the comparative series of experiments (27.55±2.32%) was closer to the control series of experiments. The same picture was observed in the study of CD4+CD25+ T-cells (the increase was from 3,77±0,42% to 7,98±0,39% (p<0,05). On the 40th day of modeling of hepatic hydatidosis echinococcosis, the total number of investigated T-cells increased. In relation to CD8+CD28+ it is possible to note the leading value in animals of the control group (15,72±1,41%). As for the dynamics of CD4+CD25+ T-cells change, we can clearly note their gradual increase between intact animals (3,95±0,35%) and rabbits of the comparison group (5,22±0,13%), and a spurt in the increase in the main series of experiments (27,94±1,15%). CD4+CD28+ T-cells prevailed (55.82±5.42%) on the 80th day of modeling of hydatidosis echinococcal cyst of the liver. The mean CD8+CD28+ T-cell content was equated to 17.21±2.64% and CD4+CD25+ T-cells were 28.11±2.32%. On the 3rd day of modeling of hydatidosis echinococcosis of the liver complicated by purulent-septic process, there is an increase of CD8+CD28+ T-cell populations up to 17,96±3,11%, against the background of decrease of other studied parameters. In the following terms the average level of T-cell percentage was equal between CD8+CD28+ (18,32±2,15%) and CD4+CD25+ (24,62±1,51%). This balance was maximally converged in animals with complicated form of the disease, whereas in animals with uncomplicated form the numerical interval was significantly higher (p<0.05).

At introduction of bacterial infection in case of reproduction of a false model with purulent-septic complication the correlation relation of the studied parameters changed, and in some cases in a radical direction. For example, the inverse correlation between CD8+CD28+ and CD4+CD28+ continued to grow (R=-0.919). CD4+CD25+ and CD4+CD28+ indices acquired inverse correlation and approached their maximum value (R=-0.989). This characterizes the immune response of the organism to the arrival of nonspecific bacterial infection. Our judgment can be proved by the value of correlation between CD4+CD25+ and

CD8+CD28+ (R=0.871), which goes from a low inverse correlation to a high direct correlation. When modeling hydatidosis echinococcosis of the liver without purulent-septic complications, the correlation value of all indicators acquires absolute direct dependence. T-cells in conditions of chronic inflammatory process acquire in dynamics expressive character increasing their immune response. High correlation significance of cellular immunity indicators was determined by high direct relationship between all investigated populations of T-cells. The maximum significance (R=0,996) was noted between changes in CD4+CD25+ and CD4+CD28+. Almost at the same level (R=0.992) was the correlation dependence between the dynamics of CD8+CD28+ and CD4+CD28+.

In the dynamics of reproduction of the experimental model of liver hydatidosis echinococcosis, the level of total IgE increased from 77.53±13.11 IU/mL to 330.19±44.91 IU/mL ($p<0.05$). The increase of IgG in blood during modeling of liver hydatidosis echinococcosis uncomplicated by purulent-septic process up to 164.92±24.17 IU/ml was more pronounced in comparison with control series of experiments (87.10±13.01 IU/ml) than in comparison series of experiments (98.15±13.68 IU/ml). A more significant value ($p<0.001$) was observed for the intensity of similar process of IgG4 in comparison with the control series of experiments (0.44±0.08 IU/mL) than in relation to the comparative series of experiments (2.23±0.12 IU/mL). Modeling of hepatic hydatidosis echinococcosis resulted in the increase of cytokines in blood IL-8, IL-9, IL-10 and IFN- γ. Such an increase of more than 10-fold was noted by us: in IL-9 relative to the control group of animals at 40 days of modeling ($p<0.001$); in IL-8, IL-9 and IL-10 relative to the control group of animals at 80 days of modeling ($p<0.001$); and in IL-9 relative to the comparison group at 80 days of modeling ($p<0.001$).

High difference in changes of CCL20 (LARC) level was noted by us on 80 days of reproduction of the experimental model of hydatidosis echinococcosis of the liver in comparison with the control group in 11,03 times ($p<0,05$). The same character of the difference (increase in 7,48 times) was noted by us in relation to the comparative group of experiments ($p<0,05$), though on 40 days of reproduction of the experimental model this difference in increase was only 5,84 times in comparison with the control series of experiments ($p<0,05$). A pronounced difference in CCL22 (MDC) increase was noted on 80 days of the course of the pathological process in comparison with the control group of experiments. Almost identical character of CCL13 (MCP-4) increase was noted by us on 40-80 days of reproduction of the experimental model of hydatidosis echinococcosis of the liver, without purulent-septic complication (5.71 and 5.47 times; $p<0.05$). A stable spurt of CCL18 (PARC) elevation was noted throughout the modeling of the pathological process from 3.42 to 3.53 times ($p<0.05$). Against this background, low significance of CCL17 (TARC) changes was noted, which was characterized first by an increase followed by regression of the activity of these chemokines. Changes in humoral immunity in animals with experimental model of hydatidosis echinococcosis of the liver complicated by purulent-septic process were expressed by a sharp jump of TNF-α production in total value in 86,51 times ($p<0,001$). It should be noted the most reliable differences ($p<0,01$) in such indicators of humoral immunity as S-IgE (9,94 times), chemokines CCL20 (LARC) (6,52 times) and cytokine IL-10 (5,77 times) emphasizing their significance in purulent-septic process. Significant differences in the production of indicators of humoral immunity corresponding to the minimum t-value accepted by us, i.e. $p<0.05$, on condition of purulent-septic process accession, were observed in relation to IgG4 (4.01 times), IL-12 (3.86 times), IFN-γ (3.68 times), IL-8 (3.6 times), IL-9 (3 times), IgG (2.65 times), CCL22 (2.54 times) and CCL13 (2.11 times).

Thus, an absolute and significant increase in CD4+CD28+ was observed in all periods of modeling of hepatic hydatidosis echinococcosis ($p<0.05$). The increase in the number of CD4+CD25+ was noted in late terms of modeling the pathological process. At the same time against this background there was a decrease in the

number of CD8+CD28+, which indicates differentiated changes in the peripheral blood mononuclear cells themselves. The expressed difference in the percentage level of T-cells CD4+CD25+ and CD8+CD28+, which took place in animals with hydatidosis echinococcosis of the liver in case of bacterial infection accession on the 7-14th day of the disease progressively decreases. This in turn indicates the dependence of cellular immune sensitivity not only on parasitic infection, but also on bacterial infection. Modeling of hydatidosis echinococcosis of the liver without purulent-septic complications leads to a sharp jump of the studied cytokines with the exception of IL-12 and TNF-α, which progressively decreased despite the development of the severity of the pathological condition. The changes occurring in the composition of chemokines are not identical in all cases during the development of hydatidosis echinococcosis of the liver complicated by purulent-septic process, however, in all cases there is a subrepressed increase in the number of CCL20 (LARC), CCL13 (MCP-4) and CCL22 (MDC). Reproduction of the experimental model of liver hydatidosis echinococcosis leads to differentiated expression of lymphocyte subpopulations, transforming the protective reaction of the organism into a peculiar immune response, which was characterized by the activity of T cells to organize the process and form a protective layer. However, this response of the organism under the action of secondary, non-specific bacterial infection changed its character of immune trace, which can be traced in the following analysis. The aggravation of the pathological process in the form of accession of purulent-septic complication of hydatidosis echinococcosis of the liver led to the development of both parallel and reverse processes in the expression of T-lymphocytes, intensifying the immunological response on the background of high sensitization of the organism. This in turn leading to the restructuring of the immunologic response of the macroorganism contributes to the load on the entire cellular population of T-lymphocytes under study.

Further work was devoted to clinical and experimental substantiation of the significance of cellular and humoral immunity indicators in predicting purulent-septic complications of liver echinococcosis. For this purpose we reveal regularities in the formation of cellular-humoral immunologic response of the organism at hydatidosis echinococcosis of the liver, provide clinical and experimental substantiation of the peculiarities of changes in cellular-humoral immunologic response of the organism at hydatidosis echinococcosis of the liver. This ultimately allows us to develop methods of predicting purulent-septic complications of hydatidosis echinococcosis of the liver. Studies have shown that animals with an experimental model of hydatidosis echinococcosis of the liver have a progressive response growth of IgG4. This response of the organism was supported by Th2-type cytokine response. With the accession of purulent-septic complications, the growth of this immunoglobulin doubles. This is due to the appropriate response of the organism to the exposure of antigens of the membrane of the daughter cell of echinococcosis. This process is based on the presence of stimulating antigens from the constituent part of the membrane of daughter larvae of echinococcus. On the basis of multifactorial analysis we proved that in conditions of progression of hydatidosis echinococcosis of the liver the dominance of T-cells of immune response, in particular - Th2 response of the organism play the leading role. In patients with regressing form of echinococcosis of the liver the dominance of Th1 immune response T-cells was observed. At the same time progression of the disease, dissemination of echinococcosis and development of residual forms is accompanied by Th2 response of the organism. According to the results of experimental studies, in the dynamics of liver hydatidosis echinococcosis development, the growth of CD4+CD28+ and CD4+CD25+ was observed. Since CD25+ is induced on both Th1- and Th2-helper cells and also present in other effector cell populations such as activated B cells, dendritic cells and monocytes, detailed studies should include high or low levels of CD25+ expression together with intracellular cytokine profiling to confirm these findings. We found that the

production of cytokines IL-8, IL-9, IL-10, IFN-γ in Th2 type occurs as an organismal response. However, in case of development of purulent-septic complications, there was a significant growth of the above presented cytokines in the order from 2 to 5 times. This increase occurred due to stimulation of peripheral blood mononuclear cells by parasitic antigens. In other words, the dynamics of the process led to increased sensitivity to these cytokines, especially to IFN-γ, the level of which reached 5-fold increases. In the dynamics of liver hydatidosis echinococcosis development there is an induction of activators of regulated chemokines CCL13 (MCP-4), CCL18 (PARC), CCL20 (LARC) and CCL22 (MDC) against the background of low activation of CCL17 (TARC). Chemokines appeared in this case to promote a Th2-cell response than Th1-cytokine-mediated granulomatous inflammation by inducing their expansion. The Th2-type chemokine CCL17 (TARC) mediates chemotactic effects on macrophages, monocytes, eosinophils, and basophilic granulocytes. CCL17 (TARC) levels are usually elevated in Th1-type inflammatory reactions, especially during the acute phase, but in the setting of septicaemia, its value was neutral and almost unstimulated, further confirming the low importance of Th1 cells. Thus, differentiated assessment of the level of changes in the studied parameters of cellular-humoral immunity in patients with liver echinococcosis once again confirmed our preliminary experimental studies and indicates the acceptability of designating them as one of the criteria for predicting complications of liver echinococcosis, including purulent-septic. Comparing the obtained clinical and experimental data, we have revealed characteristic curves of dynamics of changes in the studied parameters, which reflected the reaction of humoral response to cell expansion as a result of invasion of echinococcal hydatid cysts into the liver. By means of multifactor correlation analysis of cellular and humoral immunity indices and variants of the course of hydatidosis echinococcosis of the liver, we have developed criteria that allow predicting the development of purulent-septic complications of hydatidosis echinococcosis of the liver. The pathogenesis of such disorders is based on the degree of specific immunologic suppressiveness, which leads not only to the development of hydatidosis echinococcosis of the liver, but also to its purulent-septic complications.

Having compared all the obtained immunological data, including characteristics of their correlation and volumes of arithmetic cloud phase organization, we have developed a method of predicting purulent-septic complications based on the degree of immunological suppressiveness. At that, the levels of immunologic suppressiveness had a gradation value in the form of I-III degrees (compensated, subcompensated and decompensated). The developed scale of immunologic suppressiveness in liver echinococcosis has a numerical level for each value, which was designated by us in points and varied from 0 to 100 points depending on the degree of the lesion. Further works devoted to clinical and immunologic substantiation of the choice of methods of prophylaxis of purulent-septic complications of liver echinococcosis were carried out. The compensated degree of immunologic suppressiveness was diagnosed in 104 patients with uncomplicated form of hydatidiform echinococcosis of the liver. In 33,7% of cases (35 patients) these were patients with CE-4, in 27,9% of cases (29 patients) - patients with CL, in 26,9% of cases (28 patients) - patients with CE-3, in 10,6% of cases (11 patients) - patients with CE-1 and 1% (1 patient) - with CE-2. The subcompensated degree of immunological suppressiveness in 50% of cases (12 patients) was characteristic for hydatidotic echinococcosis of the liver with ultrasonic signs CE-1, in 37,5% of cases (9 patients) - for patients with CE-2, in 8,3% of cases (2 patients) - for patients with CL, and in 4,2% of cases (1 patient) - for patients with CE-3. We diagnosed a decompensated degree of immunologic suppressiveness mainly (93.3%) among patients with ultrasound signs of CE-2 hepatic hydatidotic echinococcosis. Only 1 patient (6,7%) with ultrasound signs of CE-1 hepatic hydatidotic echinococcosis was diagnosed with decompensated degree of immunologic suppressiveness.

Thus, the compensated degree of immunological suppressiveness was characteristic of patients with forming and dead hydatidosis echinococcosis of the liver, the subcompensated degree of immunological suppressiveness - for patients with live active parasite of hydatidosis echinococcal cyst of the liver, the decompensated degree of immunological suppressiveness - for patients with live active multichambered parasite of hydatidosis echinococcal cyst of the liver. Among the patients with complicated form of hydatidosis echinococcosis of the liver we did not reveal normal and compensated values of immunologic suppressiveness. In the majority of cases (58.94%) we revealed decompensated and to a lesser extent (41.06%) - subcompensated degrees of immunologic suppressiveness.

Summarizing the conducted comparative analysis of changes in the degree of immunological suppressiveness and clinical and laboratory signs of various forms of hydatidosis echinococcosis of the liver, we can note that in this disease the presence of a certain form of purulent-septic complication and, moreover, its manifestations in the form of signs of systemic inflammatory reaction syndrome cannot be taken as a basis for objective assessment of the patient's condition. This statement, in our opinion, is caused by the advance immune suppression, which led to the development of hydatidosis echinococcosis of the liver, as its development, and even more so its manifestation, as our experimental data showed, requires restraint of the response immune system, which was of Th2 cell type. And even under the condition of cytokinemia development, the clinical picture of purulent-inflammatory process does not reflect the whole essence of the occurring immunologic manifestations of the disease.

Only the transition to Th1 cell type of the organism's response leads to the transition to a competent type of immunologic response, contributing to the death of the parasite and its daughter cysts with the subsequent development of calcification of the focus of destruction. It is the transfer of immunologic reaction of the organism to Th1 cell type of response that should be the priority of correction of the occurring disorders. Accordingly, application of prophylactic measures to correct immunological suppressiveness will contribute to the improvement of treatment results in patients with hydatidose form of liver echinococcosis. By means of experimental studies we proved that the key role in the immunologic response of the organism is played by immunoglobulins, in particular G, which impact with antigens of the echinococcosis membrane, triggering the response of the organism according to a certain type of cellular-humoral mechanism.

At the same time, in the presence of purulent-septic complications, in conditions when the focus of destruction is preserved, all the conducted measures aimed at detoxification and correction of the detected immune disorders can be considered to be nullified due to their low efficiency.

In this connection in the main group of patients the algorithm of tactics of treatment and diagnostic measures was based on the first stage in differentiation of patients with division into subgroups with complicated course of hydatidosis echinococcosis of the liver and without complication. In case of complicated form of hydatidosis echinococcosis of the liver in a patient the measures aimed at differentiation of its type and character of affection of organs and systems of the organism with full verification of the final diagnosis were carried out. The main emphasis was placed on reducing the preoperative period and performing surgical intervention as soon as possible after patient preparation. Immediately in the postoperative period we evaluated the degree of immunologic suppressiveness, which determined our further tactics of treatment measures. In case of compensated degree of immunologic suppressiveness no special correction of the immune system was required. The generally accepted therapy was carried out, including antibacterial, detoxification and tonic treatment. At the same time, targeted antiparasitic chemotherapy was started. In case of subcompensated immunologic suppressiveness in the early postoperative period the same measures including antibacterial, detoxification and tonic

therapy were also carried out. However, along with this, correction of immunologic suppressiveness was required by means of targeted immunomodulation (thymomimetics, stimulators of antibody formation and phagocytosis). When a compensated degree of immunologic suppressiveness was achieved, targeted antiparasitic chemotherapy was started. At decompensated degree of immunological suppressiveness in the early postoperative period carried out detoxification therapy of the second level, which included plasmapheresis, hemosorption, infusion of detoxifying solutions. Metabolic and antioxidant drugs were also prescribed. In order to correct immunologic suppressiveness, in the early postoperative period we started to carry out substitutive immunotherapy (immunoglobulins, interferon alfa, thymomimetics, Roncoleukin).

This approach to therapeutic measures was carried out until the level of subcompensated or compensated degree of immunologic suppressiveness was reached, against which the targeted antiparasitic chemotherapy was started. In patients with uncomplicated form of hydatidosis echinococcosis of the liver at the first stage we diagnosed the stage of parasitic cyst development in comparison with the degree of immunologic suppressiveness of the organism. All measures, including immunomodulation and substitutive immunotherapy, were carried out according to the same scheme as in the case with the complicated form of hydatidosis echinococcosis of the liver.

After targeted antiparasitic chemotherapy for 30 days, the degree of immunologic suppressiveness was re-diagnosed.

The analysis of the effectiveness of application of the developed clinical and immunological methods of prognosis and prevention of purulent-septic complications of liver echinococcosis showed: the main share of surgical operations was closed perfect echinocolectomy, which was performed 2.1 times more often than in patients of the control group. In the main group of patients after the operation 1.2 times more often complete elimination of the residual cavity in the liver and complete reduction of the cavity was registered in 22.2% of patients. The purposeful influence on the correction of immunologic reaction of the organism allowed in the main group of patients to reduce in 1,7 times the frequency of preservation of residual liver cavity after drainage removal, in 6,8 times of purulent-septic complications. The greatest reduction of the frequency of rib osteomyelitis (4.5 times) and abscess formation of residual liver cavities (3.3 times) was achieved. The formation of intestinal and biliary fistulas was reduced in the main group of patients 2.9 times more than in the control group (from 4.4% to 1.5%). Cases of internal organs euteration were reduced 1.8 times, i.e. from 2% to 1.1%. At the same time, in the main group of patients we avoided the development of such formidable postoperative complications as peritonitis and intra-abdominal bleeding, which were noted in the control group of patients in 2.4% of cases.

Thus, as it can be seen from this comparative analysis, the application of the method of prediction and prevention of purulent-septic complications, developed by us, allowed after the correction of immunological suppressiveness of the organism to improve the regenerative properties, affecting the whole system of tissue repair, to avoid the development of complex, not seldom lethal postoperative complications. General postoperative complications in patients of the main group were noted in 3.8% of cases. Achievement of the level without general postoperative complications among the patients of the main group was achieved 1.3 times more.

In general, the application of the therapeutic and diagnostic algorithms developed by us allowed, in the main group of patients in comparison with the control group, to increase the number of good treatment results from 30,9% to 35,1%, satisfactory - from 53,4% to 56,4% and to reduce unsatisfactory treatment results from 14,8% to 8,1%, and lethality - from 1,0% to 0,3%.

Thus, the use of our developed methods of prediction and prevention of purulent-septic complications allowed in relation to the control group of patients to reduce their overall frequency

by 2.8 times, that is, from 28.2% to 10.1%, which indicates the high efficiency of our developed measures. It is also necessary to note the change in the structure of postoperative complications, in which the reduction of purulent-septic complications is clearly traced.

Already on the 3rd month of patients' follow-up complete obliteration of the residual cavity occurred in 86,8% of patients. The effectiveness of the therapeutic and diagnostic algorithm developed by us was proved once again by the low frequency of development of residual echinococcosis and absence of disease recurrence throughout the remote period of observation.

**CONCLUSIONS**

1. Despite the application of modern methods of diagnostics and treatment of hydatidosis echinococcosis of the liver, the conducted retrospective analysis of immediate results of treatment of patients of the control group showed unfortunately still high values of unsatisfactory results and lethality (14,8% and 1% respectively). In the distant period, recurrence of the disease was detected in 10.4% of patients, and in 7.4% - the presence of residual cysts. In the separated period after the operation 6 more patients died as a result of postoperative complications.

2. Analysis of changes in clinical-laboratory, biochemical and primary immunological blood parameters in patients with liver echinococcosis allows us to conclude about activation of homeostatic processes, not the least role in which is assigned to primary immunological parameters. However, these data cannot reflect the entirety of the mechanism of transformation of immunologic response, and therefore in everyday clinical practice they fall out of the field of view of clinicians. A targeted study of the correlation of T-lymphocytes, cytokines and chemokines is required, which together can reflect the stages of complex immunologic reactions of the organism in response to both parasite invasion and the development of its purulent-septic complications.

3. Reproduction of the experimental model of hydatidosis echinococcosis of the liver leads to differentiated expression of subpopulations of T-lymphocytes, transforming the protective reaction of the organism into a peculiar immune response, which was characterized by the activity of T-cells to organize the process and form a protective layer. However, this response of the organism under the action of secondary, nonspecific bacterial infection changed its character of immune trace. The indicators of humoral immunity were characterized to a greater extent by low correlation in the dynamics of pathological process aggravation, which was reflected to a greater extent in relation to chemokines CCL17 and CCL18, as well as CCL13 and CCL17. In this case, cytokines take the main determining role of the organism's response.

4. The correlation of cellular and humoral immunity indices allows to distinguish 3 phases of immunological suppressiveness development at hydatidosis echinococcosis of the liver (non-competent immune response of the organism). The first phase is characterized (compensated) by significant changes in cytokines IFN-γ and IL-9, which serve as markers of immunosuppressive state, creating conditions for invasion and growth of the parasite in the liver. The second phase (subcompensated) is characterized by a decrease in the correlation values of cytokines IL-8 and IL-10, as well as T-cell activity, which indicates disease progression. The third phase (decompensated) is characterized by a predominant increase in the activity of T-cells, increasing the production of cytokines at the expense of lymphocytes and other cells that play a key role in the purulent-septic process.

5. Transfer of immunologic reaction of the organism to Th1 cell type of response should be in the priority of correction of the occurring disorders. The key role in the development of this reaction is played by the degree of production of immunoglobulin G, which impact with antigens of the echinococcosis membrane, triggering a response of the body according to a certain type of cellular-humoral mechanism. At the same time, in the presence of purulent-septic complications, in conditions when the focus of destruction is

preserved, all measures aimed at detoxification and correction of the detected immune disorders can be considered to be nullified due to their low efficiency.

6. Application of the developed clinical and immunologic methods of prognosis and prevention of purulent-septic complications of liver echinococcosis allowed to reduce their frequency of occurrence from 28,2% to 10,1%. In comparison with the control group of patients, an increase in the number of patients with good and satisfactory treatment results by 7.2% was achieved, and the number of patients with unsatisfactory treatment results and lethality was reduced by 1.8 and 3 times, respectively.

**REFERENCES**

1. Ахмедов, Р. М., Хамдамов, Б. З., Иноятов, Х. Х., Тагаев, Ф. Х., Хамдамов, И. Б., & Хамдамов, А. Б. (2016). Эффективность применения повидон-йода при обработке остаточной полости после эхинококкэктомии печени. Наука молодых–Eruditio Juvenium, (2), 98-104.
2. Басарукин, М. А. Клинический случай гидатидного эхинококкоза печени в практике врача ультразвуковой диагностики / М. А. Басарукин, Е. Б. Петрова, Н. В. Тюрина // Радиология - практика. – 2021. – № 1(85). – С. 92-96.
3. Вафин, А. З. Влияние цитокинов на течение послеоперационного периода при эхинококкозе печени / А. З. Вафин, Е. В. Машурова // Медицинский вестник Северного Кавказа. – 2016. – № 3. – С. 13-15.
4. Дифференцированная тактика хирургического лечения эхинококкоза печени / Ш. Н. Усаров, Х. А. Умиров, Д. Б. к. Юсупалиева, Ю. М. к. Тилавова // Вопросы науки и образования. – 2019. – № 2(45). – С. 103-110.
5. Котельникова, Л. П. Эхинококкоз печени в неэндемичном регионе / Л. П. Котельникова, Г. Ю. Мокина, А. Н. Федачук // Хирургия. Журнал им. Н.И. Пирогова. – 2022. – № 8. – С. 61-68.
6. Назиров Ф.Г. Иммунологические аспекты хирургии эхинококкоза печени // Аналы хирургической гепатологии - 2019 - No 1 - С 16-25.
7. Опыт лечения эхинококкоза печени / Р. С. Шило, Э. В. Могилевец, К. С. Белюк [и др.] // Гепатология и гастроэнтерология. – 2023. – Т. 7, № 1. – С. 67-73.
8. Пути улучшения результатов хирургического лечения эхинококкоза печени на фоне цирроза / Г. В. Павлюк, Г. А. Ангелич, В. А. Морару [и др.] // Вестник Кыргызской государственной медицинской академии имени И.К. Ахунбаева. – 2023. – № 4. – С. 74-77.
9. Тоиров А. С., Хамдамов А. Б. Жигар эхинококкэктомиясидан сўнги фиброз капсула қатламидаги герминатив элементларга фотодинамик терапиянинг антипаразитар таъсирини экспериментал – морфологик асосланиши // Доктор ахборотнома. – 2022. – №3(106). – С.121-126.
10. Тоиров А.С., Хамдамов Б.З. Оптимизация методики обработки остаточных полостей после эхинококкэктомии печени с помощью лазерной фотодинамической терапии // Мутафаккир. – №3, – 2022. – С. 47-53.
11. Тоиров А.С., Хамдамов Б.З., Бабажанов А.С.,Ахмедов А.И. Эксперимент-морфологик усулда жигар эхинококкэктомиясидан кейинги қолдиқ бўшлиқга фотодинамик терапиянинг антипаразитар таъсирини асослаш// Биология ва тиббиёт муаммолари. – 2022, – №6.1(141). – С. 357-361.
12. Тоиров А.С., Хамдамов Б.З., Бабажанов А.С. Инновационный метод обработки остаточных полостей после эхинококкэктомии печени// Биология ва тиббиёт муаммолари – 2021– №6.1 (133)

– С. 376 – 379

**13.** Тоиров А.С., Хамдамов Б.З., Хамдамов А.Б. Тажрибада эхинококк натив суюқлигига фотодинамик терапия таъсирининг морфологик жиҳатлари // Биология ва тиббиёт муаммолари. – 2022, – №4 (137) – С. 249-254.

**14.** Хирургическое лечение рецидивного цистного эхинококкоза печени / А. Ю. Анисимов, А. О. Мохаммед, И. М. Оспенников, Р. М. Минабутдинов // Вестник современной клинической медицины. – 2021. – Т. 14, № 6. – С. 124-130.

**15.** Эффективность нерезекционных методов хирургического лечения эхинококкоза печени / А. О. Краснов, К. А. Краснов, В. А. Пельц [и др.] // Известия высших учебных заведений. Поволжский регион. Медицинские науки. – 2023. – № 2(66). – С. 12-21.

**16.** Эхинококкоз печени в хирургической практике / С. Н. Стяжкина, А. Е. Жернакова, Е. Л. Азимова, Н. А. Завьялова // Дневник науки. – 2021. – № 4(52).

**17.** Brunetti E., Kern P., Vuitton D.A. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop., 2020, 114 (1): 1-16.

**18.** Gentilini M., Pinon J.M. [Value of electrosynthesis (or immuno-electro-diffusion) on a cellulose acetate membrane in hydatidosis diagnosis. A comparative study with other precipitation tests]. Ann. Med. Interne (Paris), 2022, 123 (10): 883-886.

**19.** Manterola C., Barroso M., Vial M., Bustos L., Munoz S., Losada H. et al. Liver abscess of hydatid origin: clinical features and results of aggressive treatment. ANZ journal of surgery, 2023, 73 (4): 220- 224.

**20.** Ciftci TT, Yabanoglu-Ciftci S, Unal E, Akinci D, Baysal I, Yuce G, Dogrul AB, Orsten S, Akhan O, Nemutlu E. Metabolomic profiling of active and inactive liver cystic echinococcosis. Acta Trop. 2021 Sep;221:105985.

**21.** Daipert-Garcia D, Virginio VG, Oliveira FB, Siqueira NG, Ferreira HB, Rodrigues-Silva R. Evaluation of two heterologous recombinant antigens for the serological diagnosis of human polycystic echinococcosis. J Helminthol. 2022 Mar 17;96:e21.

**22.** Gentilini M., Pinon J.M. [Value of electrosynthesis (or immuno-electro-diffusion) on a cellulose acetate membrane in hydatidosis diagnosis. A comparative study with other precipitation tests]. Ann. Med. Interne (Paris), 2022, 123 (10): 883-886.

**23.** Gharbi H.A., Hassine W., Brauner M.W., Dupuch K. Ultrasound examination of the hydatic liver. Radiology, 2021, 139 (2): 459-463.

**24.** Kalra V., Dua T., Kumar V. Efficacy of albendazole and short-course dexamethasone treatment in children with 1 or 2 ring-enhancing lesions of neurocysticercosis: a randomised controlled trial. J. Pediatr., 2023, 143 (1): 111-114.

**25.** Peters L, Burkert S, Gruner B. Parasites of the liver epidemiology, diagnosis, and clinical management in the European context. J Hepatol 2021; 75:202–218.

**26.** Torgerson P.R. Transmission dinamies and control option for cysts echinococcosis / P.R.Torgerson // Parazitolosy - 2023 - Vol. 127 - P. 143-158.

**27.** Mirkhodjaev I.A., Hamdamov B.Z., Kubanov O.M. Experimental Echinococosis During Administration of Rolyaver Liposomes // Eur.Chem.Bull, - Hungary, 2023. – №12(8). – P. 8319-8321.

**28.** Mirkhodjaev I.A., Teshayev Sh.J., Akhrorova L.B. Effect of Liposomal on the Development of Experimental liver Echinococosis //American Journal of Medicine and Medical Sciences, - USA, 2023. – №13(7). – P. 910-

912.

**29.** Khamdamov B.Z., Mirkhodjayev I.A., Akhrorova L.B. Ways to improve the results of surgical treatment of lever echinococcosis // Тиббиётда янги кун, - Бухара, 2023. – №11 (61). – С. 14-17.

**30.** Hamdamov B.Z., Toirov A.S., Babajanov A.S., Hamdamov I.B., Hamdamov A.B. Laser photodynamic therapy as a method of treatment of residual cavity after liver echinococcectomy // Europe's Journal of Psychology, – 2021, – Vol. 17(3), – P. 293-297.

**31.** Khamdamov B.Z., Khamdamov I.B., Khamdamov A.B., Toirov A.S., Babajanov A.S. Laser photodynamic therapy as a method of treatment of residual cavity after liver echinococcectomy/ Биомедицина ва амалиёт журнали. – 7 жилд, – №4 сон, – 2022. –P.- 416-422. (14.00.00; №24).

**32.** Toirov A. S., Khamdamov B. Z. The Effect of Laser Photodynamic Therapy on Treatment of Residual Cavities after Liver Echinococcectomy // Ra journal of applied research. India. – Volume: 08. –2022. – P. 396-397.