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## **INFLUENCE OF DISPOSABLE RELAPAROTOMY AND PROGRAMMED SANATION ON THE EXPRESSION AND DYNAMICS OF CLUSTERS DETERMINATIONS ON IMMUNOCOMPETENT CELLS OF PATIENTS WITH ABDOMINAL SEPSIS CAUSED BY SEVERE PERITONITIS**

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### **Abstract**

Relaparotomy in the treatment of postoperative complications of abdominal surgery remains a difficult problem of modern surgery.

To evaluate the prognostic value of expression clusters of determination on immunocompetent cells of patients, the dynamics of HLA-DR + molecules and cytokines in the blood of patients with abdominal sepsis caused by severe peritonitis, as well as abscesses and phlegmons for postoperative period.

### **Materials and methods.**

The study was conducted in 40 patients diagnosed with abdominal sepsis in the period from 2017-2020, which was treated in medical institutions of Chernivtsi and Ternopil in

Ukraine, and which were divided into control and research groups. The control group consisted of 17 patients without signs of abdominal sepsis and acute surgical pathology. Determination of the expression of determination clusters such as CD11a, CD162, CD95, CD16 on immunocompetent cells, and the study of the dynamics of expression of HLA-DR + molecules and the content of cytokines IL-2, IL-4, IL-6 in the blood of patients was performed in the postoperative period. Both groups were representative by age, sex, comorbidities, risk factors. Determination of experimental parameters in the blood of patients was performed in the postoperative period (the results were evaluated before surgery, on the first, third, seventh, and on the fourteenth day of the postoperative period).

### **Research results and their discussion**

In patients with abdominal sepsis caused by severe peritonitis, the expression of HLA-DR + molecules on immunocompetent cells increases, which to some extent indicates an intensification of  $\gamma$ -interferon synthesis. At the same time, there is a sharp decrease in the content of IL-2 in the blood - the main regulator of a specific immune response.

**Keywords. Peritonitis; relaparotomy; clusters; cytokines; sepsis.**

### **Introduction**

Performing relaparotomies in the treatment of postoperative complications of surgical operations on the abdominal organs remains a difficult problem of modern surgery [1]. The literature highlights the progress in the treatment of surgical pathology, and the work on the treatment of complications in the postoperative period is isolated [2]. According to the literature, the frequency of relaparotomies ranges from 0.6 to 18% and causes high mortality - from 23 to 73% [3, 4]. Relaparotomies are performed for postoperative peritonitis, intra-abdominal abscesses, bleeding and other complications [4, 5, 6]. The question of the analysis of character of intraoperative complications, efficiency of their treatment remains actual. The problem of treatment of patients with widespread secondary purulent peritonitis is one of the most difficult and controversial in abdominal surgery [7, 8].

**The aim of the work** was to evaluate the prognostic value of expression indicators of determination clusters on immunocompetent cells of patients, the dynamics of expression of HLA-DR + molecules and cytokines in the blood of patients with abdominal sepsis caused by severe peritonitis, as well as abscesses and phlegmons to assess the postoperative period.

### **Materials and methods**

The study was conducted in 40 patients diagnosed with abdominal sepsis in the period from 2017-2020, which was treated in medical institutions of Chernivtsi and Ternopil in

Ukraine, and which were divided into control and research groups. The control group consisted of 17 patients without signs of abdominal sepsis and acute surgical pathology. Determination of the expression of determination clusters such as CD11a, CD162, CD95, CD16 on immunocompetent cells, and the study of the dynamics of expression of HLA-DR + molecules and the content of cytokines IL-2, IL-4, IL-6 in the blood of patients was performed in the postoperative period. Both groups were representative by age, sex, comorbidities, risk factors. Determination of experimental parameters in the blood of patients was performed in the postoperative period (the results were evaluated before surgery, on the first, third, seventh, and on the fourteenth day of the postoperative period).

### Research results and discussion

Studies have shown that in patients with abdominal sepsis caused by severe peritonitis, the level of CD11a + cells in the blood at the time of hospitalization was almost 6 times lower than the control, and the content of CD162 + and CD16 + cells was found, respectively. 2.8 and 2.0 times less than in virtually healthy individuals. The relative number of CD95 + lymphocytes did not change significantly (Table 1).

**Table 1.** Characterization of expression of determination clusters on immunocompetent cells of patients with abdominal sepsis caused by severe peritonitis after a single programmed rehabilitative relaparotomy ( $x \pm Sx$ )

Groups of patients	CD11a (%)	CD162 (%)	CD95 (%)	CD16 (%)
Control, (n=17)	65,12±2,49	60,47±3,05	18,36±0,93	21,45±1,12
Initial level, (n=23)	11,32±0,54 p<0,001	21,71±1,46 p<0,001	16,85±1,04 p>0,3	10,83±0,87 p<0,001
The first day after relaparotomy, (n=23)	29,73±1,26 p<0,001 p1<0,001	58,39±2,47 p>0,5 p1<0,001	21,98±1,17 p<0,05 p1<0,01	17,25±1,29 p<0,05 p1<0,001
Fourteenth day after relaparotomy, (n=23)	68,15±3,49 p>0,5 p1<0,001 p2<0,001	61,92±3,15 p>0,7 p1<0,001 p2>0,3	21,02±0,99 p>0,05 p1<0,01 p2>0,5	6,94±0,71 p<0,001 p1<0,01 p2<0,001
Notes: p - the degree of probability of differences in indicators relative to control; p1 - the degree of probability of differences in indicators relative to the initial level; p2 - the degree of probability of differences relative to the data on the first day after relaparotomy; n - is the number of observations.				

This is evidence of a deep violation of the adhesive-costimulatory interaction of immunocompetent cells in the area of inflammation. A single remediation programmed relaparotomy within two weeks effectively corrects these changes with the exception of expression on CD16 + cells, which indicates a low impact of this type of surgery on the elimination of immune complexes.

At hospitalization in patients with abdominal sepsis caused by diffuse peritonitis, there was (Table 2) an increased level of expression on immunocompetent cells of HLA-DR + molecules. At the same time, a fourfold decrease in the plasma content of interleukin-2 was observed against the background of a 35.6% increase in the concentration of interleukin (IL) - 4 and a 3.5-fold increase in the plasma level of IL-6.

**Table 2.** Dynamics of HLA-DR + molecule expression and cytokine content in the blood of patients with abdominal sepsis caused by severe peritonitis after a single programmed rehabilitative relaparotomy ( $x \pm Sx$ )

Groups of patients	HLA-DR+ (%)	IL-2 (pg / ml)	IL-4 (pg / ml)	IL-6 (pg / ml)
Control, (n=17)	16,73±0,85	216,98±10,31	224,02±11,43	219,08±9,84
Initial level, (n=23)	20,08±0,93 p<0,02	53,60±2,49 p<0,001	303,86±15,77 p<0,001	759,72±28,06 p<0,001
The first day after relaparotomy, (n=23)	18,42±1,07 p>0,2 p1>0,2	275,71±13,85 p<0,01 p1<0,001	75,29±6,54 p<0,001 p1<0,001	641,19±29,35 p<0,001 p1<0,01
Seventh day after relaparotomy, (n=23)	30,78±2,60 p<0,001 p1<0,001 p2<0,001	526,03±19,90 p<0,001 p1<0,001 p2<0,001	898,64±43,61 p<0,001 p1<0,001 p2<0,001	440,57±21,96 p<0,001 p1<0,001 p2<0,001

Notes: p - the degree of probability of differences in indicators relative to control; p1 - the degree of probability of differences in indicators relative to the initial level; p2 - the degree of probability of differences relative to the data on the first day after relaparotomy; n is the number of observations.

The concentration in plasma IL-2 increased 5 times and was 27.1% higher than that in almost healthy individuals. At the same time, the level of IL-4 in the blood decreased sharply - 4.0 times. Plasma IL-6 content also decreased. One week after relaparotomy, the expression of HLA-DR + molecules on immunocompetent cells increased again and was 1.8 times higher than the control parameters. In addition, the content of cytokines in the blood plasma

increased sharply: the level of IL-2 exceeded the control by 2.4 times, IL-4 by 4.0 times, and IL-6 by 2.0 times.

Thus, in patients with abdominal sepsis caused by severe peritonitis, the expression of HLA-DR + molecules on immunocompetent cells increases, which to some extent indicates an intensification of  $\gamma$ -interferon synthesis. At the same time, there is a sharp decrease in the content of IL-2 in the blood - the main regulator of a specific immune response. High levels of IL-4 and IL-6 in the blood indicate a switch in the immune response from Th-1 to Th-2 type, which is not biologically feasible in conditions of inflammation of the abdominal cavity.

A significant increase in the content of IL-6 in the blood, which is a neuroendocrine modulator, indirectly indicates the activation of the hypothalamic-pituitary-adrenal adaptation system.

A single programmed rehabilitative relaparotomy is quite effective in correcting disorders of cytokine regulation of the immune response: the level of the immune medium IL-2 increases on the first day, and a sharp decrease in IL-4 indicates the switching of the immune response to optimal in this period. Th-1 type. On the seventh day after relaparotomy, ie during reparative regeneration, the high level of expression of HLA-DR + molecules facilitates the recognition of foreign antigens, and the immune response is enhanced by a significant increase in blood levels of IL-2. At the same time, there is an adequate shift of the Th1 / Th2 ratio towards Th2, which generate anti-inflammatory cytokines - IL-4 and IL-6.

In patients with abdominal sepsis caused by severe peritonitis who died in the early postoperative period (Table 3), only the initial level of CD11 + cells was elevated. On the first day after surgery, the content of CD11a + cells in the blood decreased 1.7 times and was 38.2% lower than the control values. At the same time, the relative number of CD162 + -, CD95 + - and CD16 + cells still did not differ from the control. On the third day after the programmed rehabilitative relaparotomy, a total decrease in the expression of the studied clusters of determination was observed: the level of CD11a + -positive cells decreased relative to baseline by 2.3 times, CD162 + cells by 1.7 times, CD95 + lymphocytes by 1.2 times . As a result, the relative number of immunocompetent cells expressing CD11a +, CD162 + and CD16 + compared to control decreased by 1.9, 1.7 and 2.1 times, respectively.

Thus, in patients with abdominal sepsis caused by severe peritonitis, who died in the early postoperative period on the third day after relaparotomy and rehabilitation of the abdominal cavity, there is a deep violation of adhesive-cooperative intercellular interaction, as evidenced by extremely low levels of expression. cells CD11 $\alpha$  +, CD162 + and CD16 +.

**Table 3.** Dynamics of expression of determination clusters on immunocompetent cells of patients with abdominal sepsis caused by severe peritonitis who died in the early postoperative period ( $\bar{x} \pm Sx$ )

Groups of patients	CD11a (%)	CD162 (%)	CD95 (%)	CD16 (%)
Control, (n=17)	65,12±2,49	60,47±3,05	18,36±0,93	21,45±1,12
Initial level, (n=7)	78,56±3,21 p<0,01	62,85±2,89 p>0,6	18,33±0,87 p>0,9	20,94±1,34 p>0,7
The first day after relaparotomy, (n=7)	47,12±2,90 p<0,001 p1<0,001	59,10±2,11 p>0,7 p1>0,5	18,25±0,94 p>0,9 p1>0,9	17,80±0,96 p>0,06 p1>0,08
Third day after relaparotomy, (n=7)	33,84±2,02 p<0,001 p1<0,001 p2<0,01	36,00±1,93 p<0,001 p1<0,001 p2<0,001	15,38±0,62 p>0,06 p1<0,02 p2<0,05	10,07±0,53 p<0,001 p1<0,001 p2<0,001
Notes: p - the degree of probability of differences in indicators relative to control; p1 - the degree of probability of differences in indicators relative to the initial level; p2 - the degree of probability of differences relative to the data on the first day after relaparotomy; n is the number of observations.				

In addition, in patients of this group before performing a programmed relaparotomy was determined (Table 4) a fairly high (1.6 times greater than the control) level of expression of molecules of the main histocompatibility complex HLA-DR +. At the same time, the concentration of IL-2 is 4.4 times lower than the control values, IL-4 was not determined at all, while the content of IL-6 in the blood exceeded the control values by 2.2 times. On the first day after relaparotomy, the relative number of cells expressing HLA-DR + molecules decreased 1.4 times and did not differ from the control. The concentration of IL-2 in the blood was further reduced (1.9 times) and almost 9 times lower than that in healthy individuals. As before, there is no IL-4 in the blood, while the content of IL-6 increased 2.2 times and exceeded the control 5 times. On the 3rd day after surgery, the relative number of immunocompetent cells expressing HLA-DR + molecules was further reduced.

Plasma concentrations of IL-2 decreased catastrophically. IL-4 was not detected in the blood, but the level of IL-6 continued to increase and exceeded the control by 5.5 times.

**Table 4.** Dynamics of HLA-DR + molecule expression and cytokine content in the blood of patients with abdominal sepsis caused by severe peritonitis who died in the early postoperative period ( $\bar{x} \pm Sx$ )

Groups of patients	HLA-DR+ (%)	IL-2 (pg / ml)	IL-4 (pg / ml)	IL-6 (pg / ml)
Control, (n=17)	16,73±0,85	216,98±10,31	224,02±11,43	219,08±9,84
Initial level, (n=7)	27,49±1,38 p<0,001	49,71±2,05 p<0,001	not determined	480,35±23,92 p<0,001
The first day after relaparotomy, (n=7)	19,66±0,95 p>0,05 p1<0,001	25,60±1,14 p<0,001 p1<0,001	not determined	1038,30±56,86 p<0,001 p1<0,001
Third day after relaparotomy, (n=7)	15,32±0,86 p>0,3 p1<0,001 p2<0,01	10,59±0,47 p<0,001 p1<0,001 p2<0,001	not determined	1204,91±72,15 p<0,001 p1<0,001 p2>0,09
Notes: p - the degree of probability of differences in indicators relative to control; p1 - the degree of probability of differences in indicators relative to the initial level; p2 - the degree of probability of differences relative to the data on the first day after relaparotomy; n is the number of observations.				

Thus, in patients with abdominal sepsis caused by severe peritonitis who died in the early postoperative period, observed not only a decrease in the expression of HLA-DR + molecules, which complicates the processes of immune recognition, there is a deep disintegration of cytokine regulation immune response: progressive and extremely profound decrease in IL-2 content occurs in the complete absence of IL-4 in the blood on the background of a permanent and extreme increase in plasma concentrations of IL-6. That is, under conditions of suppression of the immune response due to intoxication of the patient's body, the mechanism of endogenous inhibition of the immune response "IL-6 - corticoliberin - corticotropin - corticosteroids" is additionally realized.

In patients with abdominal sepsis caused by abscesses and phlegmons (Table 5), the initial level of CD11a + and CD162 + cells is 1.7 and 1.8 times lower than the control, respectively. The relative number of CD95 + lymphocytes, in contrast, increased 1.2 times. On the first day after surgery, the content of CD11a + cells in the blood increased 1.8 times and corresponded to the control. The relative number of CD162 + cells also increased, but

remained 1.4 times lower than the control values. The content of CD95 + lymphocytes in the blood decreased 1.2 times and corresponded to that in the control group.

**Table 5.** The level of expression of clusters of determination on immunocompetent cells of patients with abdominal sepsis caused by abscesses and phlegmons ( $x \pm Sx$ )

Groups of patients	CD11a (%)	CD162 (%)	CD95 (%)	CD16 (%)
Control, (n=17)	65,12±2,49	60,47±3,05	18,36±0,93	21,45±1,12
Initial level, (n=23)	39,46±2,32 p<0,001	34,19±2,00 p<0,001	22,37±1,64 p<0,05	24,12±1,38 p>0,1
The first day after relaparotomy, (n=23)	70,23±3,74 p>0,2 p1<0,001	42,59±3,18 p<0,001 p1<0,05	18,40±0,96 p>0,9 p1>0,05	21,00±1,40 p>0,8 p1>0,1
Seventh day after relaparotomy, (n=23)	59,00±2,65 p>0,1 p1<0,001 p2<0,05	77,05±3,48 p<0,01 p1<0,001 p2<0,001	17,33±0,85 p>0,4 p1<0,02 p2>0,4	42,35±3,68 p<0,001 p1<0,001 p2<0,001
Notes: p - the degree of probability of differences in indicators relative to control; p1 - the degree of probability of differences in indicators relative to the initial level; p2 - the degree of probability of differences relative to the data on the first day after surgery; n is the number of observations.				

Thus, there is a violation of the adhesive-cooperative interaction of immunocompetent cells and increased readiness of lymphocytes for Fas-dependent apoptosis, as evidenced by the low initial level of expression of CD11a + and CD162 + and increased content of CD95 + lymphocytes in the blood. These changes in the immune system are effectively corrected by surgery: on the seventh day after surgery, the relative number of CD162 + cells and CD95 + lymphocytes is normalized with increasing blood levels of CD162 + and CD16 + cells, which provide reparative regeneration processes.

In patients of this group in the ascending period, the expression on immunocompetent cells of HLA-DR + molecules and the concentration of IL-2 in the blood corresponded to the control (Table 6). Plasma concentration of IL-4 was not determined in 50% of patients, in other patients the content of IL-4 in the blood was 13.7 times lower than the control values. Plasma levels of IL-6, in contrast, were 5.0 times higher than controls. On the first and seventh days after surgery, the relative number of cells expressing HLA-DR + molecules and



the concentration of IL-2 in the blood did not change and were equal to control values.

**Table 6.** Changes in the expression of HLA-DR + molecules and the content of cytokines in the blood of patients with abdominal sepsis, caused by abscesses and phlegmons ( $x \pm Sx$ )

Groups of patients	HLA-DR+ (%)	IL-2 (pg / ml)	IL-4 (pg / ml)	IL-6 (pg / ml)
Control, (n=17)	16,73±0,85	216,98±10,31	224,02±11,43	219,08±9,84
Initial level, (n=10)	15,60±1,19 p>0,4	199,26±9,50 p>0,2	16,32±14,00 p<0,001 not detected in 50% of patients	1085,30±79,52 p<0,001
The first day after relaparotomy, (n=10)	17,04±0,98 p>0,8 p1>0,4	203,82±12,77 p>0,4 p1>0,7	15,79±13,80 p<0,001 p1>0,9 not detected in 50% of patients	983,45±33,06 p<0,001 p1>0,2
Seventh day after relaparotomy, (n=10)	16,53±1,00 p>0,8, p1>0,5 p2>0,7	229,16±9,45 p>0,4, p1<0,05, p2>0,1	217,79±12,53 p>0,7 p1<0,001 p2<0,001	398,27±16,54 p<0,001 p1<0,001 p2<0,001
Notes: p - the degree of probability of differences in indicators relative to control; p1 - the degree of probability of differences in indicators relative to the initial level; p2 - the degree of probability of differences relative to the data on the first day after surgery; n is the number of observations.				

Thus, surgery within one week quite effectively corrects these disorders of cytokine regulation of the immune response.

**Conclusions:** Thus, in patients with abdominal sepsis caused by severe peritonitis, the expression of HLA-DR + molecules on immunocompetent cells increases, which to some extent indicates an intensification of interferon  $\gamma$  synthesis. At the same time, there is a sharp decrease in the content of IL-2 in the blood - the main regulator of a specific immune response. In patients with abdominal sepsis caused by severe peritonitis who died in the early postoperative period, there was not only a decrease in the expression of HLA-DR +

molecules, which complicates immune recognition, there is a deep disintegration of cytokine regulation of the immune response: progressive and extremely progressive in the complete absence of IL-4 in the blood on the background of a permanent and extreme increase in plasma concentrations of IL-6.

### References

1. Radzikhovsky A.P., Bobrov O.E., Tkachenko A.A. Relaparotomy. - Kiev: Phoenix, 2001. - 360 p.
2. Patel H., Patel P., Shah D. K. Relaparotomy in general surgery department of tertiary care hospital of Western India. *Int Surg.J.* 2017 Jan;4(1):344-347.
3. Omer Basol, Husein Pulat, Ismail Zihni, Sedat Damar, Ali Duran et al. Predictive factors affecting mortality in relaparotomies. *Int J Clin Exp Med.* 2016. Vol. 9(7). P. 14656-14662.
4. Syplyviy V. A., Kryvoruchko I. A., Ievtushenko A. V. Et al. Relaparotomy in the treatment of intra-abdominal complications of abdominal surgery. *Kharkiv Surgical School.* 2020. Vol. 2. P. 156-160.
5. Dziubanovskiy I.Ya., Benedykt V.V. Acute widespread peritonitis. Laparostomy or programmed relaparotomy? *Klinich. anat. ta operat. khirurg.* *Clinical Anatomy and Operative Surgery.* 2014. Vol. 13 (1). P. 53-55.
6. Endo A, Saida F, Mochida Y, et al. Planned Versus On-Demand Relaparotomy Strategy in Initial Surgery for Non-occlusive Mesenteric Ischemia. *J Gastrointest Surg.* 2020;1-10. doi:10.1007/s11605-020-04792-3
7. Van Ruler O., Boermeester M.A. Surgical treatment of secondary peritonitis: A continuing problem. German version. *Chirurg.* 2016. Vol. 87(1). P. 13-19. doi:10.1007/s00104-015-0115-8
8. Clements TW, Tolonen M, Ball CG, Kirkpatrick AW. Secondary Peritonitis and Intra-Abdominal Sepsis: An Increasingly Global Disease in Search of Better Systemic Therapies. *Scand J Surg.* 2021. doi:10.1177/1457496920984078