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ResearchArticle

CHANGES IN THE IMMUNE SYSTEM DEPENDING ON THE STAGE OFBURN DISEASE AND THE AREA OF THERMAL DESTRUCTION.IMMUNOGLOBIN REPLACEMENT THERAPY WITH GABRIGLOBIN

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ABSTRACT

In this article we consider changes in the immune system at different stages of burn disease - in acute burn shock, acute burn toxemia and septic burn. Alternative changes revealed - hyper-activation of the immune system and simultaneous development of various indicators of immunodeficiency, which was more pronounced at higher volume of thermal injury. The use of immunosupportive therapy with Ig (> 99% monomeric IgG with disintegrated structure [Russia]) for treatment of septic complications of burns and prevention of sepsis, graded patient's hyper-activation and immunodeficiency, restoring not only the shortage of IgG, but also a strong immunosupportive effect, providing more rapid relief of leukocytosis with left shift, reduction of hyper-activation immune markers, elimination of lymphocyte deficiency, IgG, B-cells and T-L, natural killer cells, cytotoxic T-lymphocytes. According to the clinical and laboratory data gabriglobin efficiency in the treatment of sepsis: 79% (without gabriglobin- 32%), with its prevention - 72% (without gabriglobin - 37%). Mortality in the treatment of sepsis - 37.5%, with conventional therapy - 46%

INTRODUCTION

One of the main causes of infection and infectious complications among burnt patients is suppression of humoral and cellular immunity[Diem, 1995]. According to Pruitt B.A. and Polk H.C. [Pruitt, Polk,1982] severe soft tissue infections often develop as a result of injury and appear to be clinical manifestations of an imbalance between immune mechanisms and microbial factors that is especially pronounced in severe burn injuries. The favorable outcome of the wound healing process largely depends on the state of the immune system of the patient [Zemskov *et al*.,2007; Fedorov *et al*., 1975]. Thereby, burn injury caused absolute T-cell deficiency and the relative scarcity of humoral immunity factors and nonspecific resistance among patients with deep burns (IIIB-IV degree) and varying degrees of lesion area [Alekseev,1993;Krutikov,2005]. Moreover, all affected by the thermal injury by the time of admission to a burn center, had a lymphocyte (L) decrease due to mature T-cells [Pivovarova *et al*.,2000], especially T-L with the expression of IL-2 receptors, whereas HLA-DR+ L were not changed, although the content of cells was growing with the expression of adhesion molecules and oxygen metabolism phagocytes. These changes were amplified by the third day of burn injury with developing deficit of IgA, while the level of IgG and IgM were not significantly changed. According to other reports there were identified morphological and structural disorders of peripheral macrophages and neutrophils accompanied by violation of their protective functions [Belockij *et al*.,1988; Karelin *et al*.,1988] - the suppression of oxygen metabolism [Alekseev,1993; Krutikov,2005] of phagocytes among burnt patients.

In this regard, it is reasonable to assume that during mass disasters leading to multifactorial lesions with a maximum

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intensity of psycho-emotional sphere of victims, immunosuppression should be much more pronounced. However, we were not able to find any studies on immune status among burnt patients, depending on the circumstances of the injury.

One of the objectives of this study was to analyze the various and numerous markers (constitutive and activation) of the three types of immune cells at various times of burn disease and depending on the area of thermal destruction. It is a unique material that was obtained in a survey of people affected by burns in a confined space, exposed thermo-inhalated injury, with damage to the CO, the strongest emotional stress, which suggests that these patients can be named "homogeneous group" on the causal factors. All patients were tested starting 1-2 days after injury, further allowing to obtain rare data of immunity status in patients affected by mass accident during burn shock and in other periods of burn disease.

The second objective of the article was to attempt to normalize changes in the immune status of burnt patients using immunosupportive therapy with gabriglobin in respect to treating developed septic complications and preventing its development. The rationale for this approach is the inclusion of intravenous immunoglobulin, which is included in the international recommendations for the treatment of sepsis [Alieshkin, Liutov,2006; Herek *et al*., 2000].

It is known that mortality among strongly burnt is 20-70%, which certainly requires expanding the range of diagnosis and treatment for this terrible state. The severity of the outcome is largely due to the development of infection, and its generalized key mechanism, which as stated above, is a change of immune system state [Alekseev *et al*.,2010]. The article focuses on this question.

MATERIALS AND METHODS

Changes in the immune system of burnt patients depending on the stage of burn disease and the area of thermal destruction

There have been 38 immunologically examined patients with burns from 0.5% to 80% of the body surface (Bs), including thermo-inhalated injury, 1-3 (burn shock- BS), 5-8 (acute burn toxemia - ABT) and 10-14 (severe burn septicotoxemia -SBS) days after the burn.

Gabriglobin treatment of septic complications of burn disease and its prevention

In this section 61 patients were examined, with burn disease in stage III and IV. 34 of them were treated with gabriglobin and represented the main group, 16 of them with burns> 30%, with developing sepsis, received 10 daily intravenous infusions of 50 mL of domestic gabriglobin, and 18 entered the sepsis prevention group with the same area burns. They received a 5-day course of immunotherapy with 50 ml of the drug. The other 27 patients out of those 61 combined in the control group without the inclusion of gabriglobin in complex therapy. They were divided into two subgroups of 13 and 14 patients; the first subgroup is a control group for primary diagnosis of sepsis set, and the second is the control group for group of generalizations of infection prevention. The main and control group of patients with the corresponding pathology were similar at diagnosis, gender and age. To evaluate the effectiveness of gabriglobin there were applied immunological methods of examination, biochemical, hematological, bacteriological analysis, the study of acute-phase reactants, and a clinical examination of patients. The effectiveness of the drug was judged by evaluating the dynamics of the clinical picture of burn disease, changes in laboratory parameters and immunogram, morbidity, and mortality rate.

Immune status was analyzed at baseline and after 5 days and 10-12-14 from start of treatment or prevention.

Gabriglobin - Human normal immunoglobulin for intravenous administration - contains 50 mL of a solution of 2.5 g of immunoglobulin G. Prevention or treatment course was 5-10 infusions every 24 h.

All patients were analyzed for oxygen metabolism of neutrophils by chemiluminescence (CL) on a luminometer L1251 (LKB, Sweden), reinforced by addition of $1 \cdot 10^6$ M of luminol and 25 mM lucigenin induced by zymosan, opsonized 10 mcl of blood serum of healthy donors for 30-40 min, expressing it in mV / 100 phagocytes (neutrophils in terms). Oxidation in the presence of luminol made it possible to determine the intracellular generation of reactive oxygen species in the presence of lucigenin - revealing only the extracellular generation of superoxide anion oxygen. The concentration of immunoglobulin A, G and M in serum was determined using monospecific antisera AO NPO "SINTEK" turbidimetry method for semi-automatic analyzer Screen Master Plus firm «Hospitex Diagnostics S.A.»(Switzerland) at a wavelength of 340 nm.

Phenotypic analysis of immunocompetent and phagocytic cells was performed by flow cytometry using monoclonal antibodies (mAbs) of the company «BD Biosciences, Becton, Disckinson and Over.» (USA) by the prescription of the company, on a flow cytometer BD FACSCalibur, using 50 mcl of whole blood followed its treatment with mAb (CD3, CD4, CD8, CD16, CD21, CD11b, CD25, CD4+CD25+, CD3+HLA-DR+, CD64, CD70), labeled with FITC (fluorescein isothiocyanate) or dual labeled FITC / PE (phycoerythrin), determination of immune index CD4 / CD8 and removing erythrocyte lysis buffer. Additionally, for the identification of granulocyte monocyte subpopulations of cells expressing the various markers labeled with FITC, «stained" their respective mAb or CD66B, CD14, labeled with PE.

Statistical Analysis

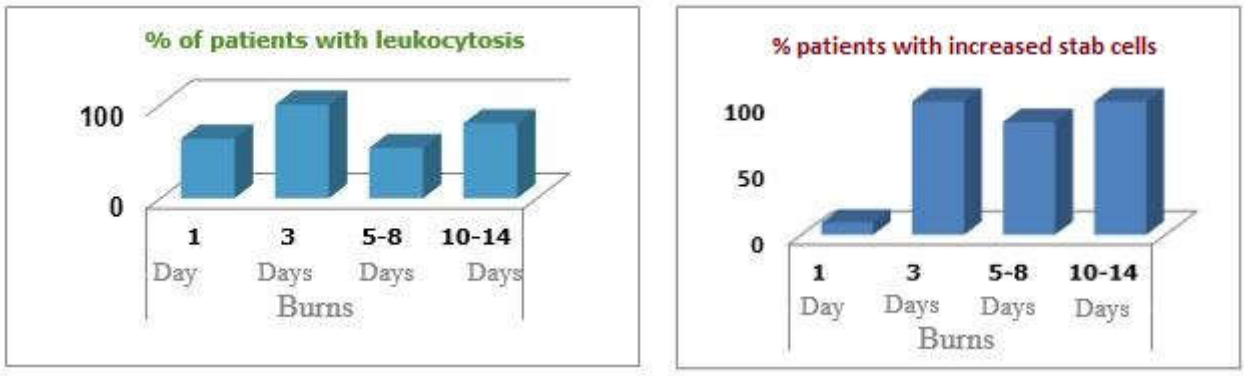
Collected data was assessed by double statistic analysis. First, we determined the relative number of patients with deviating immune parameters between groups of significant differences with 2-3 levels of immunodeficiency or immune stimulation according to an established statistical method [Zemskov *et al*.,1997].Secondly, used in the calculation of indicators of immune differences criterion χ^2.

RESULTS AND DISCUSSIONS

Changes in the immune system of burned patient due to degree and area of thermal destruction

Leukocytosis developed rapidly in a burned patient, even on 1 and 3 days at 63.6% and 100% of patients, it decreased a little following ABT and SBS periods, maintaining quite high levels in 53.8% and 80% of patients (Fig. 1a).

1st day it was noticed in 54.6% of patients, but on the 3rd – in all of patients. Further lacking continues in ABT and SBS periods in 84.6% and 60% of patients respectively (Fig. 3a).



a **b**

Fig. 1 % of Leukocytosis patients (a) and patients with left shifted leukogram (b) during different stages of burn disease.

Correlation between the factor and burned area was less clear: highest leukocytosis level in the case of large burn area – 42-70% – was noticed in BSh (1st day) period in 80% of patients comparing to smaller burns – 28-35% – in 50% of such cases.

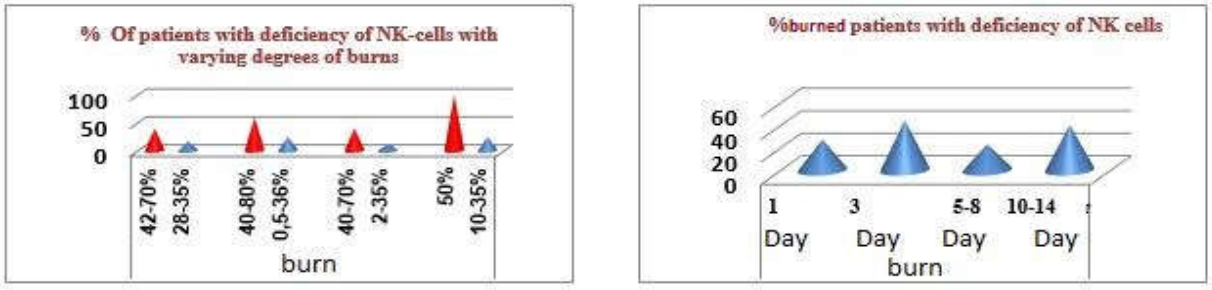
Great left shift of leukogram developed in BSh period even on 3rd day in all patients and remained high level in ABT (5-8 days) and SBS (10-14 days) periods in 84.6-100% of cases (Fig. 1b).

Dependence between leukogram shift and burn area was less exact and was noticed only in cases of huge burn (42-70%) in 20% of patients, while in cases of small burn area (28-35%) there were no leukogram shifts in a single case.

Severe lack of natural killer cells developed rapidly – in BSh period on 1st day – in 27.3% of patients, in 44.4% on 3rd day, and remained strong in ABT and SBS periods (up to 3.2 – 2% NK-cells) in 23.1% and 40% of cases respectively (Fig.2a).

It was noticed, that in cases of large burn area a lack of the protein was stronger too – in 60% of patients with 42 - 70% area of burn in the first day of BSh, in ABT and SBS periods in all of patients with the same area and 50% (Bs), with smaller area – 50%, 75% and 50% of cases. Importantly, strength of the lack was greater in cases of bigger burn areas (Fig.3b).

So, with 40-80% area of burn and 0.5-36% even on 3rd day in BSh period, the median value of IgG in all groups of patients was 0.6 gram\liter and 1.35 g\L, with 40-76% and 2-35% on 5th-8th day of ABT period – 2.06 g\L and 4.3 g\L. Finally, on the 14th day in SBS period with 50% and 10-35% – 4.5 g\L and 8.35 g\L (normal value). Deep lack of IgG was noticed in all the cases, especially in patients with big areas of burn, we examined that using the immune system disorder formula developed by us: count started from the minimal healthy level (7.2 g\L) and arranged 2-3 stages of deep immune disorder [13].



a **b**

Fig. 2% of burned patients with NK-cells deficit depending on stage (a) and area (b) of burn disease.

Lack of NK-cells was clear in most cases of large burn area. On 1st, 3rd, 5th-8th and 10th-14th days with 42-70%, 40-80% and 50% burn areas it was noticed in 40%, 60%, 40% and 100% of patients respectively. In cases of smaller areas – 28-35%, 0.5 – 36%, 2 – 35% and 10 -35% only in 16.7%, 25%, 12.5% and 25% respectively (Fig. 2b). Value of χ^2 in this case reached 13,3; 24,9; 19,43 and 116,24. I.e. in all cases the assurance reached high level, amounting $P< 0.001$.

It is notable that progression of burn disease is marked by fast developing strong lack of IgG even in BSh period, when on the

Phagocyte oxygen metabolism increased rapidly after a burn even in BS period – on 1st and 3rd days it was noticed in 36.4% and 44.4% of patients, in ABT and SBS in 61.5% and 60% of patients respectively (Fig. 4a), moreover the bigger the area of burn, the greater increase was Fig. 4b.

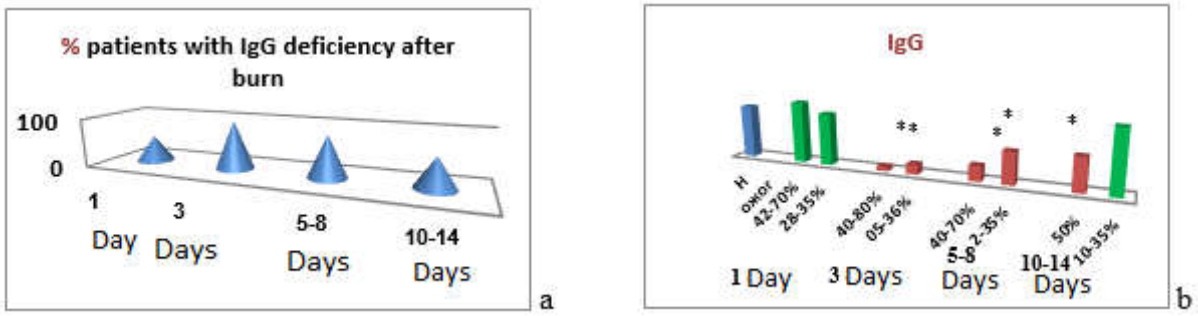
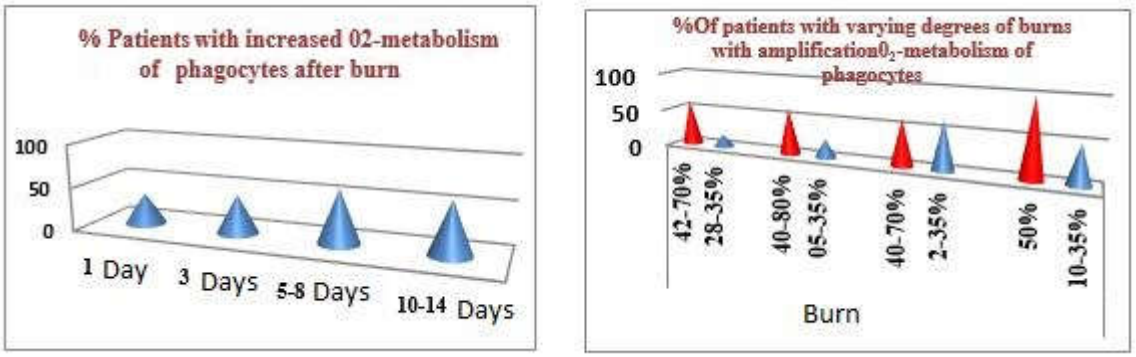


Fig. 3 % Of patients with a lack of IgG depending on stage (a) and area (b) of burn disease. N- normal, * a significant decrease, 1st – 14th day after the burn



a **b**

Fig.4 % of patients with increased phagocyte oxygen metabolism after a burn depending on stage (a) and area (b) of burn disease on 1st, 3rd, 5th-8th and 10th-14th days.

Phagocyte oxygen metabolism increased in BSh period on 1st and 3rd days in 60% of patients with 42-70% and 40-80% area of burn, in cases of 28-35% and 0.5-35% areas increase was noticed in 16.7% (χ^2= 39.5; P <0.001) and 25% (χ^2= 24,9; P <0.001) of patients respectively. In all the cases during SBS period and 50% Bs area, but with 10-35% area – only in 50% of cases.

Also under burn injury increase of granulocyte (Gr) with an expression of activation marker CD64+ (high-affinity Fcγ–receptor), sometimes even in the first few hours there was peak achievement on the 3rd day in all of the patients. However later in ABT period – 5th-8th days it was still high in 92.3% of patients, and on 10th-14th days decreased rapidly, such that it was still noticed only in 20% of patients (Fig.5). Yet correlation between amount of CD64+Gr and area of burn injury wasn't well defined.

Lack of cytotoxic T lymphocyte developed rapidly – even in BSh period on the 1st and 3rd days, so did in ABT and SBS periods on 5th-8th and 10th-14th days – in 36.4%, 11.1%, 38.5% and 60% of patients respectively, except that the well-defined correlation between area and the lack of was noticed only in SBS periods on 10th-14th days – with 50% Bs area – in 100% of cases, with 10-35% area - in 50% of cases.

Finally, the same situation was noticed with rapid development of HLA-DR+ monocyte deficiency (HLA-DR+ Mn) starting from the first few days of burn disease.

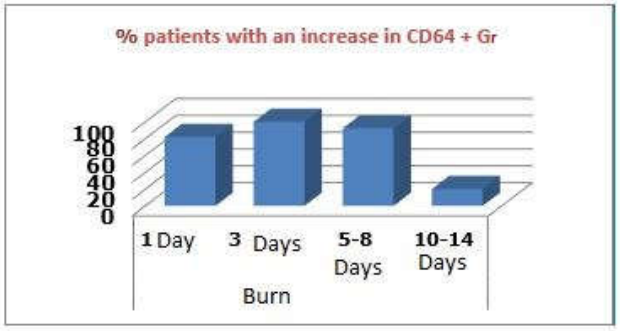


Fig. 5% of patients with increased CD64+ Gr (expression of activation marker CD64+ (high-affinity Fcγ–receptor) during different stages of burn disease.

The lack decreased rapidly after SBS period on 10th-14th days, and correlation between the lack of HLA-DR+ Mn and the area was the same as with the lack of cytotoxic T lymphocytes – with 50% Bs area lack was noticed in 100% of patients, and with 10-35% area – only in 25%. It was mentioned that deficient development of B- lymphocytes, T- lymphocytes, T-helpers, increase of granulocyte with an expression of activation of lipopolysaccharide and endotoxins receptors (CD14+).

Thus, both in BSh and ABT periods various immune disorders stay on. As well as in SBS period, when it's obvious that persistent disorders require immunosupportive and immunotropic therapy.

Especially difficult immune status disorders were noticed in patients with major heat-inhalational injury and combustion products CO toxicosis. For the first time in our practice, except

for major immune disorders, we noticed a total absence of IgG in the circulation of some burn patients, which obviously required instant immunosupportive therapy.

Therefore, these examinations allow us to draw a conclusion that in cases of big area of injury, and in particular in cases of mass damage, pervasive and multidirectional immune changes in burned patients take place. Basically, two different parallel and alternative processes go on – excessive activation of immune system (leukocytosis with left shifted blood formula, sharp increase of granulocyte with an expression of activation of lipopolysaccharide and endotoxins receptors, high-affinity Fcγ–receptor, increase of oxygen metabolism, functional activity of HLA-DR+ monocyte and deep lack (natural killers, lymphocytes, cytotoxic T-lymphocytes, T-helpers, B-lymphocytes, IgG).

The bigger the area, the greater the lack of IgG, natural killers and phagocyte oxygen metabolism (oxidative stress, that means hyperactivation of phagocyte system) will be.

Obtained results clearly belong to predictive personalized preventive medicine, as they give us a tool for targeted immunotherapy.

This therapy was performed, and then burn patients underwent immunosupportive therapy with IgG, as mentioned, without any aggregated clusters, and with fully saved biological features and subclass composition. We chose IgG – gabriglobin [Latyisheva, Setdikova, 2005], because it has not only immunosupportive activity, but it has huge immunomodulating activity. Its ability to neutralize toxins involves 106 types of antibodies of pathogen and semipathogen originators, and nosocomial infections [Romanov *et al*., 2010].

Treatment of septic complications of burn disease with gabriglobin and its prevention

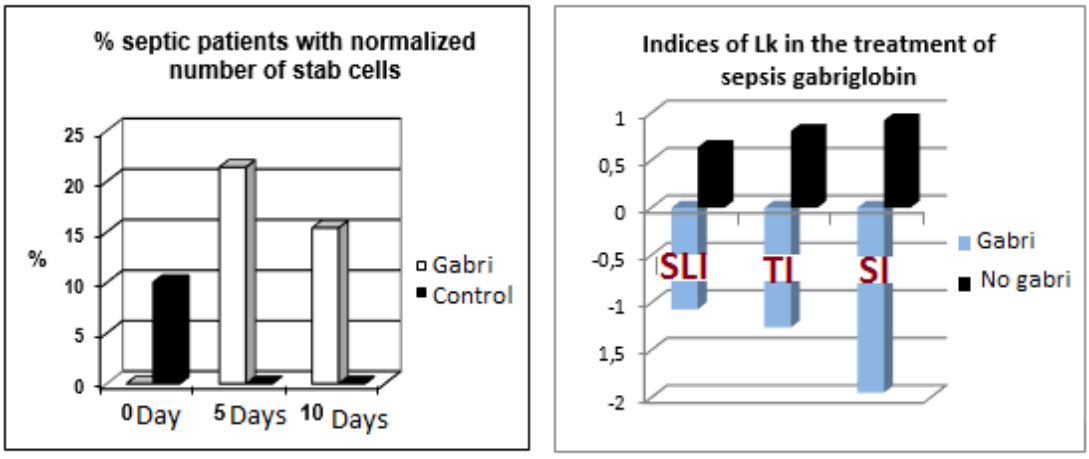
Group with burn sepsis

Initially, immunosupportive therapy was used for treatment of onset sepsis.

hasn't been identified. Meanwhile, when determining the blood normalized index shift to the left in both groups significant differences were found. For example, in Figure 6a it canbeseen clearly a decrease in blood formula with a shift to the left in terms of the normalized analysis of the content of stab granulocytes. This reflects the absence of the reference period in patients with normal value stab granulocytes and their steady rise after the therapy with gabriglobin, whereas the control kinetics of the group was the reverse - original period indicated a small number of patients with normal stab cells, but more patients with normal values of these cells remained, as all noticed their elevated levels. Equally striking was the difference in terms of endogenous intoxication, which increased in the general 3-8 times higher than normal. In the group with gabriglobin all indices declined sharply (SLI- shift of leukocytes index; TI- toxic index damage of leukocytes; and SI – shear index)in comparison with indices intoxication patients. But receiving gabriglobin (Figure 6b), which increased in all cases, i.e. the drug caused a decrease hyper-activation of the immune system.

Reducing the hyperactivation of the immune system under the influence of therapy with gabriglobin is also revealed in the example of the contents of cells expressing the activation markers CD70 +, entering the superfamily of tumor necrosis factor. Its sharp reduction in the study group was much higher than in the control group of patients with sepsis who were not receiving gabriglobin (Fig.7).

It is very important to note that the use of gabriglobin eliminated or leveled deep deficiency of a number of immune parameters compared with patients in the control group. In 70% of the patients with sepsis group, it was observed that deep relative lymphopenia (X = average value of 8% of total lymphocytes) combined with absolute lymphopenia in 30% of patients. After treatment with gabriglobin in 61.5% of patients there was a normalization of lymphocytes in contrast to the control group not receiving gabriglobin, - 75% of patients in this group maintained profound lymphopenia (Fig.8a).



ab

Fig. 6 Decrease blood formula shift to the left (a) and indices of endogenous intoxication (b) under the influence of treatment of sepsis gabriglobin. The control patients did not receive gabriglobin

Analysis of the immune status at baseline in all patients with burn sepsis observed a sharp leukocytosis of 13.2 to 23.8 billion / l (X = 15.5 billion / l), however, significant differences in leukocytes between the groups gabriglobin receiving or not,

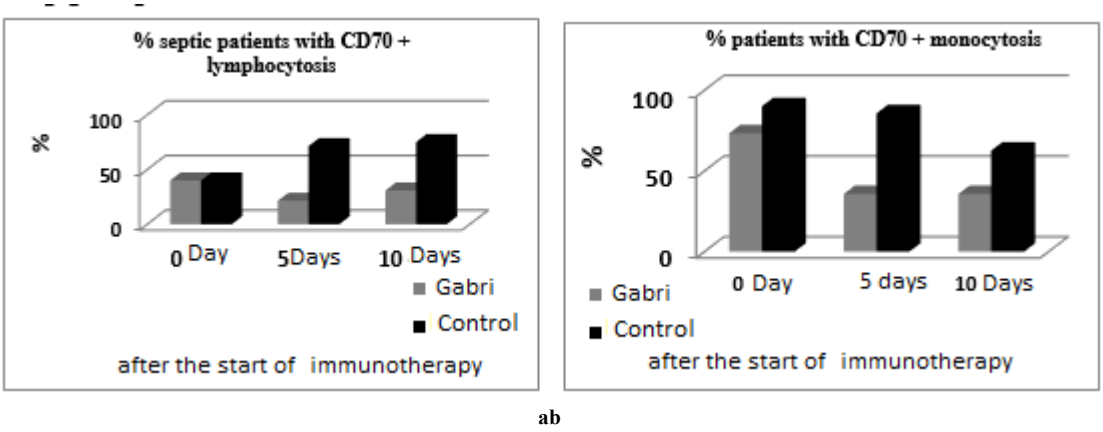


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Fig. 7 Reduced lymphocyte hyperactivation (a) and monocytes (b) patients withsepsis influenced treatment of gabriglobin

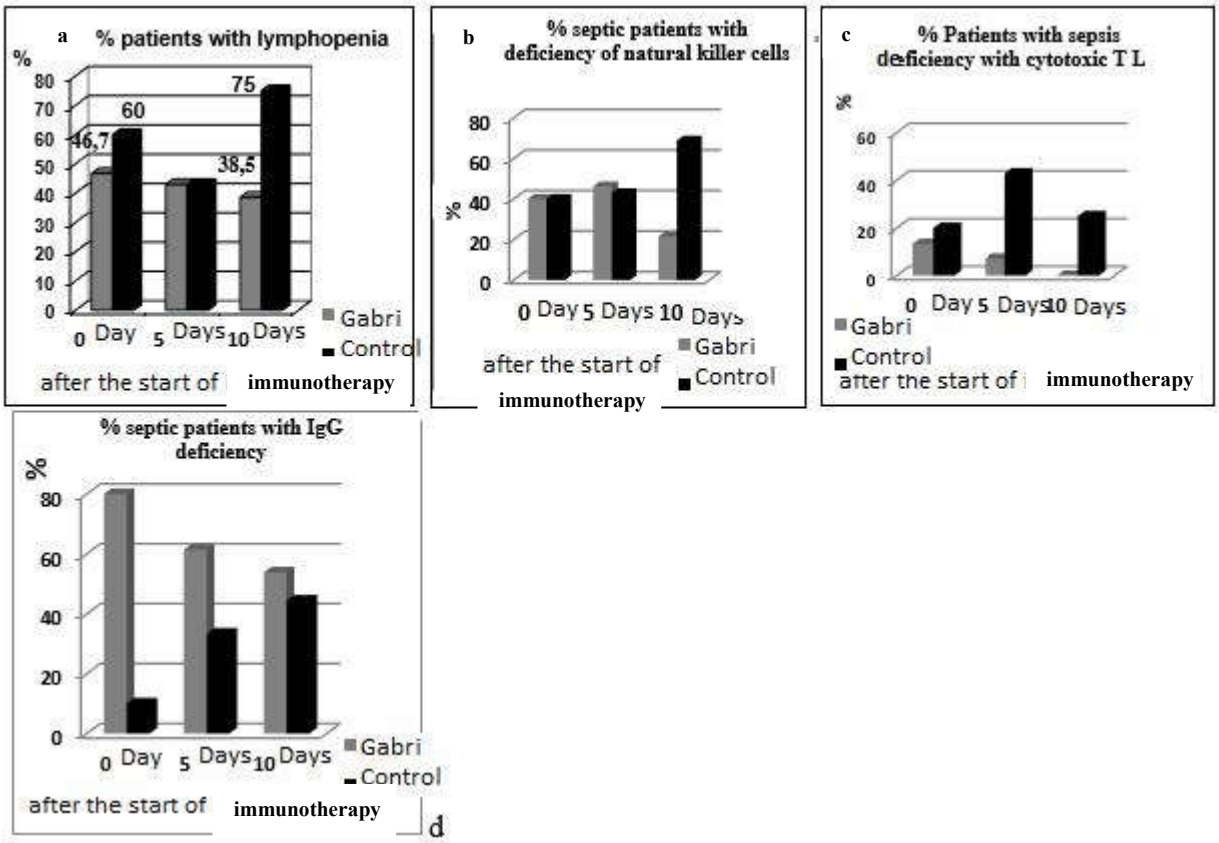

Fig. 8 Reduced lymphocyte deficiency (a), natural killer (b) and cytotoxic T-L (c) and IgG (d) in patients with sepsis treatment influenced gabriglobin.

In the test group during the treatment with gabriglobin a sharp decrease in the number of patients with a deficiency of natural killer cells (Fig. 8b) was noticed, which was 3.21 times greater in the control group. Moreover, after applying gabriglobin the number of patients with deep deficiency killer cytotoxic T-lymphocytes dramatically decreased up to their complete disappearance for 11 days after initiation of treatment, while in the control group, rate of such patients was much higher (Fig. 8c).

A number of patients who maintained a deficit of T-cell components (T cells, helper T cells, cytotoxic T-lymphocytes), died.

Note that in the group of patients with sepsis at baseline in 53% the deep deficit of HLA-DR+ monocytes (indicating a pronounced inflammatory process development) was observed, which after immunosupportive therapy with gabriglobin was recovered in 75% of patients.

At the same time reduced levels of monocytes with the expression of HLA-DR was observed in all patients with thermo-inhalated injury, which, of course, exacerbated the severity of the condition, and a reduced level of this marker was 60% and 50% of patients who died respectively in the experimental and control groups that confirmed their critical condition and poor prognosis.

In the main group in the initial period before the introduction of gabriglobin 80% of patients had a deep deficit of IgG (X = 3.98 g / L), and even deeper in patients with combined thermo-inhalated injury, the same is registered among dead patients (Fig. 8d). In the control group the suppression of baseline IgG was noted only at 10%, and by the end of the observation, it had already registered in 44.4% of patients with very low levels of IgG, so it was observed in 75% of patients who died. Kinetics of IgG content was completely different in patients and control group. Thus, in the group of patients who did not receive gabriglobin, the percentage of patients with deficiency of IgG steadily increased, the main group with immunoglobulin it declined sharply. This is despite the fact that in the initial period of the patients of the main group the number of patients with deficiency of IgG was much higher than in the control (8 times). This indicates that the main group of patients there was initially more severe damage to the immune system than in the control group.

Group of prevention of infection generalization

The criteria for inclusion of gabriglobin in the therapy of these patients were: the emergence of leukocytosis with a shift to the left, band neutrophils, relative lymphopenia (X = 11.3%), increase in CD64 + marker from 34 Gr to 99.8% (X = 72.4%) in 93.2% of patients, a sharp decline in the level of IgG (X = 3.2 g / l), the activation of the oxygen metabolism in the overwhelming number of patients up to 19.35 - 40 mV / 100 phagocytes (X = 24.65 mV / 100 phagocytes) which suggests the possibility of joining the infectious complications.

As in the treatment of established sepsis in the group, prevention also decreased hyper activation of the immune system.

Thus, a generalization of infection prevention group is that there was a decrease of increased amounts of leucocytes with the mean value in the group from 11.83 to 8.38 billion / l, and in the control group (average in the group) maintained prophylaxis marked leukocytosis more (X = 12, respectively, 87 and 10.42 billion / l), and in the main group after 10 days among all patients was only 14.3% of patients with leukocytosis, whereas in the control at the same time - 44.4% (Figure 9a). Gabriglobin caused more rapid relief of neutrophilic left shift from 9.6 to 5.8%, in control, it has not changed, so X = 12.27 and 10.83%, and the main group of patients on the 10th day with the sharp shift was 42.9% in the control group - 88.9% of patients (Figure 9b.). Moreover, gabriglobin prevention caused a clear reduction of elevated toxic indices of endogenous intoxication leucocytes (9e).

In the main group of patients receiving gabriglobin 5 days in a row, reducing the average value of granulocytes in the group with a marker CD64+ marked with the initial period to 10 days

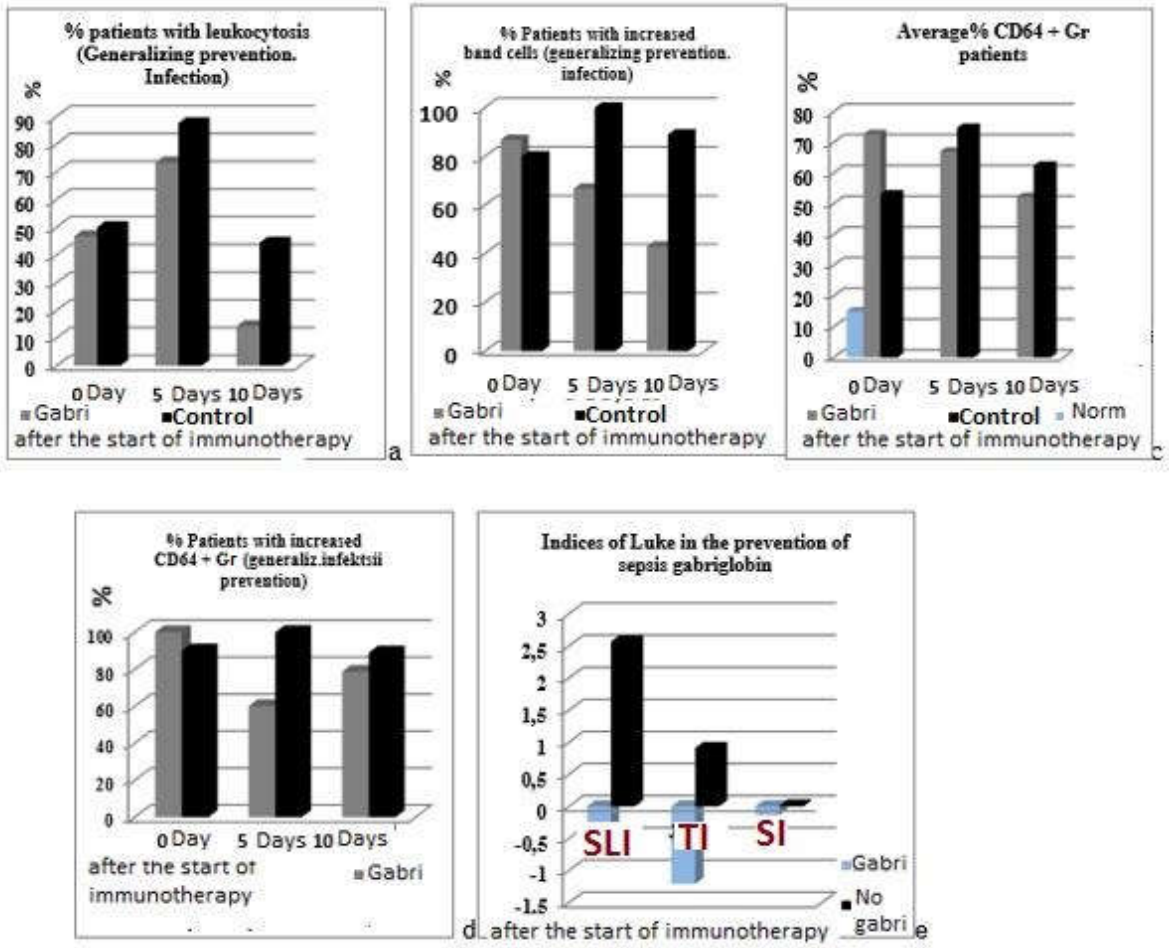

Figure 9 Reducing the high content of leukocytes (a), the shear formula Blood left (b) and CD64 + granulocytes (c and d), the weakening of endogenous intoxication.[(e)→"Luke" - leukocytes].

after initiation of treatment with 72.74 to 52,2% CD64+ - granulocytes, and in the group without their gabriglobin the average value (for patients) remained in the same period high - respectively X = 53.1% and 62.4% (9c), while the number of patients with a high content of CD64+ granulocytes on the 5th day of sepsis prevention was the main and control groups, respectively, 60% and 100% (Fig. 9d).

Under generalization of infection prevention, when applied, gabriglobin also observed a significant reduction of hyperactivation of the immune system in comparison to the control group in which the patients did not receive immunosupportive therapy with gabriglobin and against other immune parameters. On the 5th day after the gabriglobin course (10th day from the start of therapy) in the test group 40% of patients had an increased content of HLA-DR+ T cells, whereas they proved 76% in the group without gabriglobin, in patients with elevated values of CD70+ - neutrophils these figures were respectively 33% and 88% of patients.

However, the content of lymphocytes expressing IL-2 receptors (CD25+ cells) that reflect activation of the immune system of the Th1-cell type can be considered as positive compensatory response antibacterial protection in conditions of deficiency of the humoral system also shown to be elevated in 40% of patients receiving gabriglobin, compared with a control group of patients - without immunotherapy of patients where it was only 12.5% (Figure 10a.).

Aswellasinthegroupwithsepsisinpatientswithinfectionpreventiongeneralizationgabriglobinapplicationwasaccompaniedbynormalizationorlevelingdeficitnumberofimmuneparameters.

A low level of IgG in patients in the control group generalization preventing infection at baseline and at the end of observation was observed in 40% and 33.3%patients, while in the initial period of the main group of patients it was recorded at 93.3%, and after treatment gabriglobinitrecovered completely in all patients (Fig. 10b).

Moreover, if the deficit of natural killer cells in the prevention group treated gabriglobin, in the initial period was observed in 20% of patients after treatment of only 7.7% left, whereas in the control group of the same figures without immunotherapy in the same period amounted to 40 and 33.3% of patients (Fig. 10c).

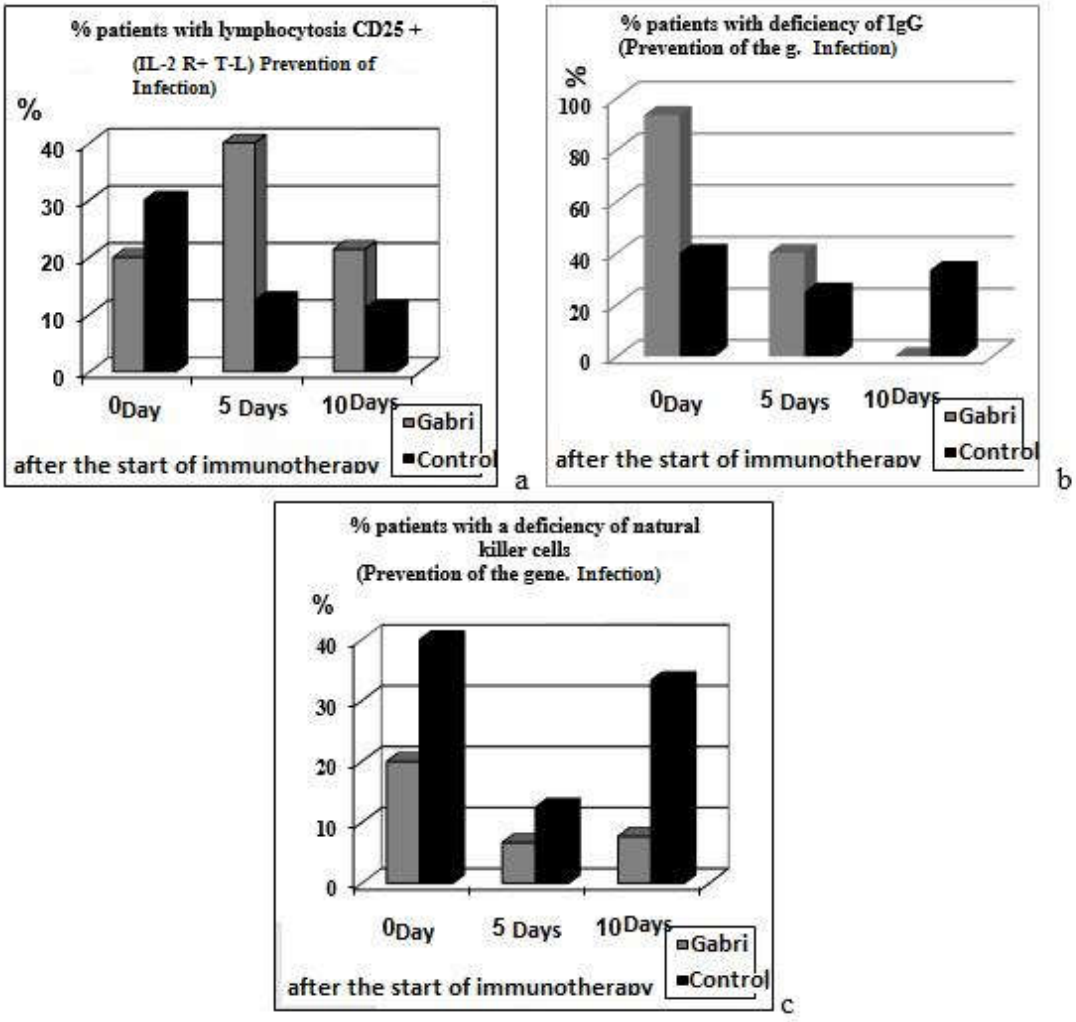

Figure 10 Leveling CD25 + lymphocyte deficiency (a), IgG (b), NK-cell current (c) in patients with sepsis prophylaxis gabriglobin.

In evaluating the clinical efficacy of gabriglobin we used a modification of the scale developed for sepsis and septic complications [Cheliabinskaiagorbolnitza № 1, 2011] (Table. 1).

Table 1 Clinical efficacy of gabriglobin in sepsis and prevention

Goodeffect	Satisfactoryeffect	Noeffect
Reducing severe clinical condition to moderate	—	—
Normalization of temperature, or if the hecticintermittent - a decline of 1 ° C	Reducing t ° C to low grade, if the hectic or intermittent, the reduction of <10^{0}C	No difference with conventional therapy
Respiratoryratedecrease ≥4/мин	Reduced respiratory rate to <4 / min	—
Heart rate reduction >10% (from base)	Reduced heart rate <10% (from baseline)	—
Blood pressure increase >15% or its stabilization	The lack of stabilization of blood pressure	—
Increased blood protein not less than 5 g / l, but not from outside the administration	Increasedproteinemia <5 g / l	—
Normalization of platelets or increased by 30%	Slight increase of platelets <30% (from baseline)	—
Reducingleukocytosis> 15%	Reducingleukocytosis<15%	—
Reducingproteinuria≥ 50%	—	—
Dynamics of the procalcitonin level in the treatment and prevention versus initial		—

We take into account the total efficiency (good and satisfactory effect) and no effect. The results are shown in Figure 11.

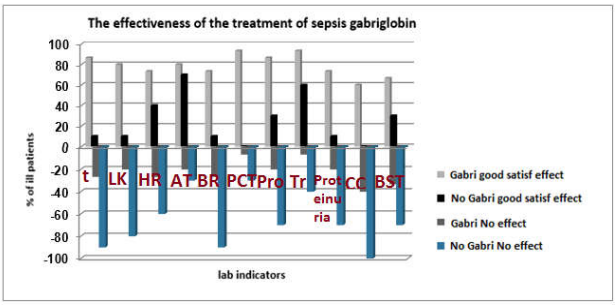

Fig. 11a The effectiveness of the treatment of sepsis by gabriglobin in burned patients.

Legend:

“Gabri good satisf effect” – good and satisfactory effect while using Gabriglobin

“No Gabri good satisf effect” – good and satisfactory effect while using alternative treatment

“Gabri no effect” – there is no effect while using Gabriglobin

“No Gabri no effect” – there is no effect while using alternative treatment

t - temperature, LK - leukocytes, HR- heart rate, AT – arterial tension, BR – breath rate, PCT – procalcitonin, Pro – total protein rate, Tr – thrombocytes, “Pro (Prot) – proteinuria”, CC – velocity of clinical conditions changes from severe to mid-severe, BST- erythrocyte sedimentation rate

They show (Fig. 11a), that all the 11 clinical and laboratory parameters for the overall "good and satisfactory efficiency" (changes in temperature, leukocytosis, heart rate and respiratory rate, blood pressure, total protein, procalcitonin and platelets, proteinuria, and erythrocyte sedimentation rate,and positive changes in clinical condition) [Tab. 1] was a significant difference between the groups of patients who received gabriglobin and did not receive it. In the first case, 79% of patients with sepsis to immunotherapy with gabriglobin reacted positively, while the second to the traditional treatment without immunoglobulin - only 32%; not responded to treatment 21% of patients in the first group and 68% in the second, i. e. efficiency immune replacement therapybygabriglobin in sepsis was 79%.

Suffice it to similar results obtained with gabriglobin for the prevention of infection generalization (Fig. 11b).

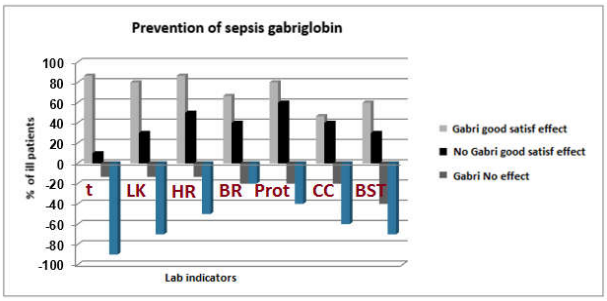

Fig. 11b Prevention of sepsis by gabriglobin. The notation is the same.

Figure shows that the overall clinical effectiveness gabriglobin estimated from the positive changes (Table 1 -. "A good effect + satisfactory effect") temperature, leukocytosis, heart rate and respiratory rate, total protein, to improve the clinical condition and the BST was 72%, one traditional therapy - 37%; respectively, were observed in the effectiveness of treatment

group, 28%, and in the second (non-treated gabriglobin) - in 63% of patients.

Consequently, the use of gabriglobin for the treatment and prevention of sepsis assessment at all indicators is effective.

This is clearly seen in the indices and the shift of white blood cells, reflecting endogenous intoxication. In the case of the treatment or prevention of sepsis infection generalization effect it was absolutely obvious - use gabriglobin accompanied by a decrease in the values of all indexes (TI, SLI and SI) from baseline (at figure there are conventionally negative values, Figure 6b, 9e.). Whereas in the groups with traditional therapy realized a different trend - constant increase (positive values in the figure) of all indices in comparison with the baseline values.

CONCLUSION

Thus, the use of gabriglobin for treatment of sepsis or preventing generalization of infection in patients with burns in comparison with the control group without the inclusion of this drug provides rapid reduction in the shift of blood to the left, reducing the immune hyperactivation markers (02-metabolism of phagocytes, cells with markers CD70+, CD64+, HLA-DR+ T- L) reduces or eliminates the deficiency of total lymphocytes, IgG, B-cells and T-lymphocytes, natural killer cells, cytotoxic T lymphocytes, that is killer and cytotoxic cell capacity. These data indicate that immunosupportive therapy has a strong immunomodulatory effect in not only restoring the original deficit of IgG, but also normalizing the deficit or hyperactivation of a number of key immune parameters. Moreover, gabriglobin therapy is also quite effective in the evaluation of clinical and laboratory data of burn sepsis in the treatment (an average of 79%), and for its prevention - an average of 72% of cases, it is accompanied by a decrease in endogenous intoxication, whereas conventional therapy without immunoglobulin strengthened it, as assessed by the dynamics of SLI values, TI, SI.

References

1. Diem E (1995) Infections in burns. 7th European congress of clinical microbiology and infectious diseases: Abstr. Vienna, Austria. 15.
2. Pruitt BA, Polk HC (1982) Burns and soft tissues. Infection and the surgical patient. ChurchillLivingstone.; 4: 113-131.
3. Zemskov AM, Zemskov VM, Korotkih IN, Zemskov MA, Korotkih NN (2007) Immunnyerasstrojstva I ihkorrekcijaprignojno-vospalitel'nyhprocessah (Immune disorders and their correctionatpyo-inflammatory processes). Moscow: Triada-X.
4. Fedorov VD, Rivkin VL, Gurseva HF, Martynova TN (1975) Sovremennyevzgljadynatechenieranevogoprocessa I lechenie ran (Modern views on the course of wound healing and thetreatment of wounds). Hyrurgija. 4: 136-141
5. Alekseev AA (1993) Ozhogovyj sepsis: diagnostika, profilaktika, lechenie (Burn sepsis: diagnosis, prevention, treatment). Dissertatcyadoktoramed. nauk. Moscow
6. Krutikov MG (2005)Infekcija u obozhzhennyh: jetiologija,patogenez, diagnostika, profilaktika I lechenie (Infection at the burnt: etiology, pathogenesis, diagnosis, prevention and treatment). Dissertatcyadoktora med. nauk. Moscow
7. Pivovarova LP, Ariskina O., Assur MV i dr. (2000) Immunologicheskij status i ego korrekcijau postradavshih s ozhogovymsepsisom(Immunological status and its correction in patients withburn sepsis). XIX Congress chyrurgovUkrainyi.Sbornicnauchnyihtrudov. Kharkov: 337-338.
8. Belockij SM, Snastina TI, Filjukova OB (1988) Mikrobnyjfaktor v hemiljuminiscenciinejtrofilovperifericheskojkrovibol'nyh s gnojnojhirurgicheskojinfekciej (Microbial factor in the chefmiluminescence of peripheral blood neutrophils of patients with purulent surgical infection). Zh. Mikrobiol., Epidemiol.,Immunobiol. 8: 87-90.
9. Karelin AA, Alekseev AA, Globa AG i dr. (1988) Jenzimaticheskajaprodukcijasuperoksidapolimorfnojaderny milejkocitamichelovekapriozhogovojbolezni (Enzymatic production ofsuperoxide by polymorphonuclear leukocytes at a burn human disease). Vopr.med. himii. 5: 107-110.
10. Alieshkin VA, Liutov AG (Ed.) (2006) Klinicheskoieprimenenieimmunoglobulinadliavnutrivenno govvedeniagabroglobin (Clinical application of intravenous immunoglobulingabriglobin). Posobyoedliavrachei. Moscow: Meditsina
11. Herek O, Ozturkk H, Ozyurt M, *et al* (2000) Effects of treatment with immunoglobulin on bacterialtranslocation in burn wound infection. Ann Burns Fire Diseases.Vol.XIII. № 1.Internet.
12. Alekseev AA, Krutikov MG, Yakovlev VP. (2010) Ozhogovaiainfektcia(Burn infection).Moscow: Publishing House of the book High school.
13. Zemskov AM, Zemskov VM, Zoloedov VI (1997) Dostupnyiemetodikiocenki I correctciiimmunnyihnarushenii u bolnyih(Available methods of evaluation and correction of immune disorders in patients). KlinicheskayaI laboratornayadiagnostika.N3C: 3-4.
14. Latyisheva TV, Setdikova NX (2005) Novyiotechestvennyi immunoglobulin G - gabriglobin vcompleksnoiterapiibolnyihobsheivariabelnoiimmunnoined ostatjchnostiu (New nativeimmunoglobulin G - gabriglobin in the treatment of patients with common variable immunodeficiency). VestnikRossiiskoivoenno-medicinskoiakademii: 1 (13) s. 41-43
15. Romanov VA, KulibinAYu, Zaitzeva IP (2010) Antibacterialnieantitela v immunoglobulinachI civorotkachkrovicheloveka: vzgliadiznastoiaschego v proshloie (Antibacterial antibodies and immunoglobulins in the blood serum of a person: a view from the present to the past) Zh. Mikrobiol., Epidemiol.,Immunobiol. №5, c. 40-43
16. Cheliabinskaiagorbolnitza№ 1 (2011)Otchetpoeffectivnostigabriglobinaprisepsise I egoprofilactike (Performance Report gabriglobin in sepsis and prevention). Internet