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ABSTRACT

of the dissertation for the degree of Doctor of Sciences

**CLINICAL - PROGNOSTIC VALUE
AND CORRECTION OF IMMUNE DISORDERS IN
GASTRODUODENAL BLEEDING OF ULCERATIVE
GENESIS**

Specialty: 3213.01 - Surgery

Field of science: Medicine

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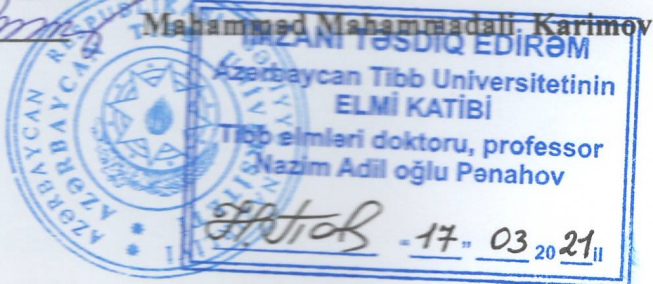
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GENERAL DESCRIPTION OF THE WORK

The urgency of the problem and productivity rate. At the beginning of the XXI century, on the background of the successes of modern medicine and the development of modern technologies, the treatment of patients with acute gastroduodenal ulcerative bleeding (AGDUB) continues to be a serious problem in gastroenterology. Despite the high effectiveness of conservative treatment of peptic ulcer, which occurs in 7-10% of the population of developed countries, among the complications, 42–47%¹.

At the present stage, in AGDUB, the overall mortality rate reaches 5.0–16.0%², and the level of postoperative mortality is 5.5–25%³⁴.

Currently, in many cases, diametrically opposite approaches and broad spectrum of methods and methods that have a local and systemic effect on the ulcer are used to treat peptic ulcer disease and achieve final hemostasis. However, in 10.1–19.1% of patients relapse of bleeding occurs⁵ and in such cases the death reaches higher levels. Although the success of endoscopic hemostasis and therapy significantly reduces the surgical activity, the surgical treatment in acute gastroduodenal bleedeng will not lose its significance. On the other hand, in AGDUB, the choice of the duration of surgery and the method of operation continues to be controversial.

¹ Кубышкин В.Н., Петров Д.Ю., Смирнов А.В. Методы эндоскопического гемостаза в лечении язвенных гастродуоденальных кровотечений // – Москва: Хирургия, – 2013. №9, – с. 67-72

² Holster I., Kuipers E. Management of acute nonvariceal upper gastrointestinal bleeding: current policies and future perspectives // World J Gastroenterol., –2012, v. 18 (11), – p. 1202-1207

³ Сажин В.П. Лечение больных с высокой вероятностью развития рецидивов язвенных гастродуоденальных кровотечений / В.П. Сажин, В.М. Савелев, И.В. Сажин [и др.] // Хирургия, – Москва: – 2013. №7, – с. 20-23

⁴ Бойко В.В., Криворотко И.В., Грома В.Г. Результаты и проблемные вопросы лечения острых язвенных желудочно-кишечных кровотечений за последние 15 лет // – Харьков: Харківська Хірургічна Школа, – 2016. №2 (77), – с. 141-145

In AGDUB, the process of evolution of medical tactics from maximum conservatism towards radicalism once again shows that the assessment of the risk of recurrence plays a key role in the choice of surgical tactics. After endoscopic hemostasis, earlier prediction of recurrence of bleeding (RB), the selection and optimization of treatment tactics require more accurate criteria of risk factors (RF) and early diagnosis of RB. However, despite the successes of modern conservative therapy and the widespread use of endoscopic hemostasis due to the existence of a “technological threshold”, there are no opportunities to influence the ways of the causes of RB – the progression of morphofunctional changes in the ulcer¹². In this regard, the weakest link in the tactics of modern treatment is the impossibility of preventing and the difficulty of early diagnosis of the RB³. Existing modern forecasting systems of RB⁴ in practice do not completely justify themselves.

In recent years, based on the research, despite evidence of the significant role of immune and antioxidant disorders in the pathogenesis of a multifactorial systemic gastroenterological disease of peptic ulcer, including AGDUB⁵, there is no consensus in assessing the changes taking place and the methods for adequate correction.

¹ Кубышкин В.А. Организация и результаты хирургической помощи при язвенном гастродуоденальном кровотечении в стационарах центрального федерального округа / В.А. Кубышкин, В.П. Сажин, А.В. Федоров [и др.] // – Хирургия, – Москва: 2017. №2, – с. 4-9

² Sostres C, Lanas A. Epidemiology and demographics of upper gastrointestinal bleeding: prevalence? Incidence and mortality // *Gastrointest. Endosc. Clin N Am.*, – 2011, v. 21(4), – p. 567-581

³ Шапкин Ю.Г., Потахин С.Н. Динамика основных показателей лечения язвенных гастродуоденальных кровотечений: анализ многолетних наблюдений // – Саратов: Саратовский научно-медицинский журнал, – 2014. Т.10, №3, – с. 456-460

⁴ Лебедев Н.В. Сравнительная оценка систем прогноза рецидива язвенного гастродуоденального кровотечения / Н.В. Лебедев, А.Е. Климов, П.Ю. Соколова [и др.] // Хирургия, – Москва: – 2013. №8, – с. 28-31

⁵ Hacıyev C.N. Xora mənşəli kəskin qastroduodenal qanaxmalar zamanı cərrahi müdaxilənin orqanizmin antioksidant statusuna təsiri / C.N. Hacıyev, V.A. Allahverdiyev, M.R. Quliyev [və b.] // – Bakı: – Cərrahiyyə, – 2015, №3, – s.16-20

It is known that the integral participants of immune responses, universal regulators of intercellular connections and endogenous immunomodulators secreted by immunocompetent cells, cytokines play a crucial role in the homeostatic regulation as a common system of the body

Cytokines as a new independent self-regulation system along with regulation of proliferation, differentiation and functions of immune system cells also actively participate in numerous functions of the body, in particular in the transfer of intercellular signals, in the formation and regulation of protective reactions, and determine the characteristics of the formation of an adaptive immune response. However, the peculiarities of the cytokine profile and the correction of the revealed changes in peptic ulcer disease, including those in AGDUB, have not been sufficiently studied. It should also be noted that the data obtained are contradictory and do not allow conclusions to be drawn about the direction of immunological processes.

Despite numerous studies in AGDUB, depending on the degree of bleeding, local and systemic indicators of immune, cytokine and antioxidant status, the relationship between local and systemic cytokine profile, as well as the relationship between immunity, cytokine profile and antioxidant status are not well understood. In addition, there is no way to more accurately predict recurrence of bleeding. On the other hand, until today, within the framework of complex treatment of AGDUB, a unified strategy has been developed for schemes and methods for conducting cytokine therapy and correction of peroxidation disorders, depending on the degree of bleeding, the depth of changes in immune, cytokine and antioxidant statuses. In this regard, the solution of all the above-mentioned problems is an important and very urgent task from both theoretical and practical points of view.

Purpose of the study. Improving the results of treatment of patients with acute gastroduodenal bleeding of ulcerative genesis by developing individual prediction of bleeding recurrence using a fuzzy module method taking into account violations of the cytokine profile of homeostasis and correction of cytokine imbalance.

Objectives of the study.

1. Assess changes in cellular and humoral immunity, depending on the severity of blood loss in patients with acute gastroduodenal bleeding.

2. To conduct a comparative study of pro-inflammatory and anti-inflammatory cytokines in the blood, gastric juice and urine of patients with ulcers of the stomach and duodenum, complicated by acute bleeding, depending on the degree of its severity.

3. To study the correlation between the cytokine profile indicators with cell and humoral chains of the immunity in acute gastroduodenal bleeding of ulcer etiology.

4. To develop methods for individual correction of cytokine profile disorders depending on the severity of blood loss in acute gastroduodenal bleeding and to study the effectiveness of cytokine therapy using betaleukin.

5. To evaluate the efficiency of transplantation of progenitor cells of cord blood to the cytokine profile.

6. To study the state of antioxidant status depending on the degree of blood loss in patients with acute gastroduodenal bleeding, to determine the relationship between the cytokine profile and lipid peroxidation products, to evaluate the effectiveness of differentiated antioxidant therapy.

7. To develop a method for individual prediction of the probability of recurrence of bleeding using a fuzzy module created on the basis of the theory of fuzzy logic and an algorithm for the tactics of differentiated individual active treatment.

8. Introduce an integrated approach program in the treatment of acute gastroduodenal bleeding into the clinic using the fuzzy module method that reliably predicts relapse of bleeding in each patient, as well as an algorithm that allows you to choose an individual method of treatment for each patient, as well as on the SAPS scale, the degree of anesthetic risk on the ASA scale in addition to this algorithm for the correct choice of the volume of operation.

Methods of research: The dissertation work was carried out in several stages with rigorous planning. At the first stage, the current issues in this area were studied by analyzing the scientific works of

domestic and foreign scientists.

In the second stage of the study, the results of the treatment of 1501 inpatient patients were analyzed - 891 patients retrospectively and 610 patients prospectively. The severity of bleeding in all patients were analyzed by methods of A.A. Shalimov and V.F Saenko (1987), the intensity of bleeding was analyzed by J.A. Forrest (1974) classification and severity of patient condition were evaluated on the SAPS scale.

In the third stage of the study, patients in the prospective group were studied T-and B-immunity, antioxidant status, and cytokine profile indices in the blood, depending on the type of treatment. At the same time, the cytokine profile and some of the antioxidant status parameters have also been investigated locally. All this was accomplished at the highest methodological level using modern equipment.

In the fourth stage of the study, it was developed fuzzy module according to Loutfi Zade's fuzzy logic theory and analyzed the implications of its clinical application.

The results obtained in the fifth stage of the study were based on modern statistical methods.

The patients analyzed prospectively were divided into comparison (I) and basic (II) groups. The comparison group included 123 patients who received standard conservative therapy (subgroup Ia), 57 patients who underwent surgical intervention and received baseline therapy (subgroup IA).

In the subgroup IIa of the main group, 107 patients underwent conventional chemotherapy and cytokine therapy and antioxidant treatment with mexidol. In the subgroup IIb, Betaleukine and Mexidol were included in the treatment complex of 63 patients against the background of surgical intervention. Of the 10 patients in the IIc subgroup, only $20 \cdot 10^6$ numbers of progenitor cells were transplanted in the postoperative period.

Scientific novelty:

- For the first time in AGDUB, through the development and clinical application of a fuzzy module method based on the theory of fuzzy logic, the most reliable individual prediction of bleeding recurrence was achieved.

- For the first time in patients with AGDUB, a relationship was found between the degree of blood loss and indicators of both parts of the immune system.

- For the first time, depending on the degree of blood loss, in a comparative aspect, local and systemic cytokine profile indicators were evaluated.

- For the first time in AGDUB, the relationship between indicators of immune, cytokine and antioxidant status was studied.

- For the first time in the surgical treatment of AGDUB, the clinical and immunological significance of transplantation of cord blood progenitor cells has been proven.

- For the first time, in conservative and surgical treatment of AGDUB taking into account the depth of cytokine imbalance and the degree of blood loss, the effect of directed systemic cytokine therapy was studied in dynamics using differentiated doses of recombinant IL-1 β - betaleukin on the immune status and cytokine imbalance.

- For the first time, taking into account the role of local indicators of the cytokine profile, the clinical and prognostic significance of these indicators in the occurrence of recurrence of bleeding was determined.

- For the first time in a variety of biological environments, a direct relationship between the level of IL-6 and the severity of the condition of patients was determined in dynamics.

- A complex program based on the fuzzy module method, reliably predicting bleeding recurrence, was developed and clinically applied, based on an algorithm, allowing the choice of an individual treatment method for each patient, as well as on the algorithm of correct selection of the patient's volume according to the severity of the patient according to the SAPS and ASA scales .

- Compared with traditional methods, high clinical efficacy of integrating systemic cytokine therapy with Betaleukin and antioxidant therapy with Mexidol in individual and differentiated order was proved in a comprehensive program of conservative and operative treatment of AGDUB, taking into account the depth of cytokine imbalance, the intensity of lipid peroxidation processes and the degree of blood loss.

Theoretical-practical significance:

– The results obtained during the study have provided further augmentation of theoretical knowledge about the disorders that occur in the underlying mechanisms of cytokine status in the AGDUB.

– For AGDUB, the fuzzy module method is developed and introduced into clinical practice predicting the risk of bleeding recurrence most accurately.

– An algorithm has been developed and introduced into clinical practice that allows increasing the possibilities of conservative and surgical methods of treatment in AGDUB for each specific patient, with a correct definition of the indications for surgery contributing to significantly improving the results of treatment.

– Inclusion of basic therapy into the complex both in conservative and surgical treatment in a differentiated individual dose of Betaleukin and Mexidol, taking into account the depth of immunosuppression and cytokine imbalance, as well as the intensity of lipid peroxidation processes, which have a normalizing effect on the immune status and cytokine profile of the body, as well as enhancing antioxidant protection and eliminating endogenous intoxication makes it possible to significantly improve the results of treatment.

– In patients with AGDUB, taking into account the depth of primary changes in local and systemic indicators of immunity, cytokine profile and antioxidant status, conducting in the early period for each patient in an individual differentiated order directed immunocorrection and antioxidant therapy helps eliminate immunosuppression and cytokine imbalance, and inhibits free radical processes.

– The proposed comprehensive systemic approach to patients, taking into account the developed algorithm and the results of fuzzy module, the severity of the condition on the SAPS and ASA scales, allows choosing the right individual treatment tactics, determining the dynamics of immune, cytokine and antioxidant status indicators, as well as endogenous intoxication markers to evaluate the effectiveness carried out therapy.

– The definition of the level of IL-6 in various biological media in the postoperative period allows determining the individual prog-

nosis of the outcome of the disease.

The implementation of the results. The results were introduced into the clinical practice of medical institutions in Baku, in the Department of General Surgery and Anesthesiology of the Azerbaijan Medical University, Clinical Medical Center, Republican Clinical Hospital named after M. Mirkasimov and SI of "Institute of General and Emergency Surgery. V.T. Zaitsev AMS of Ukraine "(Kharkov).

The main provisions of the dissertation research are used in the course of teaching general surgery and anesthesiology of the Azerbaijan Medical University, as well as hospital surgery at the Kharkov National Medical University.

Connection of research with problem plans of medical sciences. The dissertational work was performed in the framework of the research work plan of the Department of General Surgeons and Anesthesiology of the AMU (No. State Registration No. 011404053) on the basis of an agreement with the State Institution "Institute of General and Emergency Surgery named after V.T. Zaitsev of AMS of Ukraine "(Kharkov).

The main scientific theses for the defense

1. The AGDUB is characterized at the systemic and local level by immunosuppression of T- and B- immunity, cytokine imbalance, intensification of lipid peroxidation processes and the depth of these changes directly depends on the degree of blood loss.

2. Systemic cytokine and antioxidant therapy with Betaleukin and Mexidol, having a normalizing effect on immunosuppression and cytokine imbalance, accelerates the dynamics of the stabilization of lipid peroxidation processes.

3. Targeted immunocorrection with recombinant IL-1 β -Betaleukin and antioxidant therapy with Mexidol in AGDUB is a pathogenetically substantiated, effective and promising method of treatment, proven by clinical, laboratory, immunological and biochemical studies.

4. On the background of targeted immunotherapy with Betaleukin, antioxidant therapy with Mexidol by potentiating the effects of various mechanisms due to the effects on the immune system and metabolic processes stabilizes lipid peroxidation, increases the num-

ber of immune cells, accelerates the recovery of cytokine balance, improves biochemical parameters of the blood.

5. In AGDUB on the background of complex basic therapy, intravenous transfusion of cryopreserved cord blood cells as a pathogenetically based method of treatment eliminates deep immune deficiency and cytokine imbalance as soon as possible and also has a positive effect during the postoperative period.

6. In AGDUB, the developed algorithm allows a differentiated approach to each patient and specifically select an individual treatment strategy.

7. Developed on the basis of the theory of fuzzy logic and introduced into clinical practice, the method of fuzzy module in patients with AGDUB more reliably predicts the risk of recurrence of bleeding in the hospital.

Approval of the thesis. Fragments of the thesis were presented, discussed and reported at a number of Republican and international scientific, scientific and practical conferences: 19 Ulusal Cerrahi Kongresi (Türkiye, Antalya, 2014), Türk Hepatopankreatobilier Cerrahi Kongresi (Türkiye, Antalya, 2015), International Congress "EuroMedica-2015 (Hannover, Germany, 2015), Nauch. practical conf. dedicated to 100th prof. A.M. Alizade (Baku, 2015), XII International Scientific and Gastroenterological Session (St. Petersburg, 2015) and 20 Ulusal Cerrahi Kongresi (Türkiye, Antalya, 2016), at the meeting of the Academic Council (13.01.2017, protocol №1) "The Institute of General and Emergency Surgery named after V.T. Zaitsev AMS of Ukraine "(Kharkov) and at the interdepartmental meeting of the Department of Surgical Diseases and in the Educational-Surgical clinic of AMU (14.04.2017), as well as in the approbation committee of the Dissertation Council D 03.011 conducting scientific seminars at AMU (03.07.2018, protocol №11), at the Scientific Seminar of the Dissertation Council (25.02.2020, protocol №1) operating under the ED 2.06 of AMU.

Publications. On the topic of the thesis were published 46 papers. Of these, 24 journal articles, 25 theses.

The scope and structure of the thesis. The thesis consists of an introduction (16181 characters), review of the literature (80208 char-

acters) 4 chapters (368019 characters), conclusion (42944 characters), conclusions, practical recommendations and a list of references. The work is presented on 411 pages of computer text, illustrated with 80 tables, 26 figures and 64 graphics. References include 48 domestic and 352 foreign sources.

THE CONTENT OF THE WORK

Material and methods of research. The basis of the research was the results of observation, comprehensive examination and treatment of 1501 patients with AGDUB who were hospitalized to the Department of General Surgery and Anesthesiology of Azerbaijan Medical University and to the Institute of General and Emergency Surgery. V.T. Zaitsev "of the Academy of Medical Sciences of Ukraine (Kharkiv) from 2010 to 2014. The results of treatment of 891 and 610 patients were analyzed retrospectively and prospectively in a comparative manner. In retrospectively analyzed patients, active individual was used, and in prospectively analyzed patients, active differentiated individual tactics were used. Of the 1501 patients, 1054 ($70.2 \pm 1.2\%$) were men.

It should be noted that the overwhelming majority of patients - 1267 people ($84.4 \pm 0.9\%$) were of working age, and the number of patients of old age was 359, which accounted for $23.9 \pm 1.1\%$ of the total number of patients.

When analyzing the duration of the disease, patients with an ulcer history up to 5 years amounted to 535 ($35.6 \pm 12\%$) people, 6-10 years - 568 ($37.8 \pm 1.3\%$) patients, and over 10 years - 271 ($18.1 \pm 1.0\%$) patients, "mute" ulcers were detected in 127 ($8.5 \pm 0.7\%$) patients. It should be noted that in 127 ($8.5 \pm 0.7\%$) patients, especially in the elderly and old, the ulcer was diagnosed for the first time, and the disease was characterized by a "dumb" course.

In 1090 patients ($72.6 \pm 1.2\%$), a duodenal ulcer was observed, in 310 ($20.7\% \pm 1.0\%$) patients with a stomach ulcer, and in 101 ($6.7 \pm 0.7\%$) patients - combined ulcers of the stomach and duodenum. 1369 patients had one, 101 patients had two, and 31 patients had "mirror" ulcers. So, in 1501 patients 1633 ulcers were identified.

Ulcers localized in $74.0 \pm 1.1\%$ of cases on the lesser curvature, on the anterior and posterior walls of the stomach and duodenum were complicated by bleeding. In $26.0 \pm 1.1\%$ of cases, ulcers of other gastroduodenal areas were identified.

In 123 ($8.2 \pm 0.7\%$) patients the ulcer had diameter of less than 0.5 cm, in 694 ($465.2 \pm 1.3\%$) - 0.5-1.0 cm, in 511 ($34.0 \pm 1.2\%$) - 1.1-2 cm and in 115 patients ($7.7 \pm 0.7\%$) - 2.1-3.0 cm, and in 58 ($3.7 \pm 0.5\%$) cases the diameter of the ulcer was over 3.0 cm. We consider gastric ulcers with a diameter of 1.5-2.5 cm and duodenal ulcers 1.1-2.0 cm large, and stomach ulcers more than 2.0 cm and duodenal ulcers more than 3,0 cm - gigantic. So, 684 ($45.6 \pm 1.3\%$) patients had ulcers with a diameter of more than 1.1 cm.

All patients were admitted to the hospital as a matter of urgency. But the time between the onset of bleeding and admission to the hospital was different. So, 231 ($15.4 \pm 0.9\%$) were admitted to the clinic in the first three hours, 271 ($18.1 \pm 1.0\%$) within 4-6 hours, 353 in the period 6-12 hours ($23.5 \pm 1.1\%$), within 12-24 hours - 267 ($17.8 \pm 1.0\%$), 24-48 hours - 198 ($13.2 \pm 0.9\%$), by 2-3 day - 95 ($6.3 \pm 0.9\%$) and after 3 days - 86 ($5.7 \pm 0.6\%$) patients. Thus, $25.3 \pm 1.1\%$ (379) patients were admitted to the clinic within 24 hours from the onset of bleeding.

The degree of blood loss was assessed by the method of A.A. Shalimov and V.F. Saenko (1972). Overall, 576 ($38.4 \pm 1.3\%$) patients had mild, 623 patients ($41.5 \pm 1.3\%$) had moderate severity, and 302 ($20.1 \pm 1.0\%$) patients had severe degree of blood loss. 527 ($35.1 \pm 1.2\%$) patients had hemorrhagic shock.

In patients admitted to hospital, bleeding intensity was evaluated according to the classification of J. A. Forrest (1974). Based on this classification, from retrospectively analyzed patients, 46 ($5.2 \pm 0.7\%$) showed bleeding with a pulsating jet (FIa), 64 ($7.2 \pm 0.9\%$) showed bleeding flow (FIb), and 189 ($21.2 \pm 1.4\%$) of cases of (re-cent) bleeding that occurred on the background of a thrombosed vessel (FIIa), 146 ($16.4 \pm 0.9\%$) patients had a fixed thrombus clot (FIIb), in 220 ($24, 7 \pm 1.4\%$) observations on the background of stopped bleeding, hematim sediment at the bottom of the ulcer (FIIC) and 226 ($25.4 \pm 1.5\%$) patients had an ulcer with a clean (white) bot-

tom (FIII).

The intensity of bleeding in the prospectively analyzed patients was as follows: FIa - 31 ($5.1 \pm 0.9\%$), FIb - 42 ($6.9 \pm 1.0\%$), FIIa - 139 ($22.8 \pm 1.7\%$), FIIb - 112 ($18.4 \pm 1.6\%$), FIIc - 136 ($22.3 \pm 1.7\%$), FIII - in 150 ($24.6 \pm 1.7\%$) patients. In general, the intensity of bleeding in patients was as follows: from 1501 in 77 patients ($5.1 \pm 0.6\%$) FIa, in 106 ($7.1 \pm 0.7\%$) - FIb, in 328 ($21.9 \pm 1, 1\%$) - FIIa, in 258 ($17.2 \pm 1.0\%$) - FIIb, in 356 ($23.7 \pm 1.1\%$) - FIIc and in 376 ($25.1 \pm 1.1\%$) - FIII .

Of 1501 patients, 203 ($13.5 \pm 0.9\%$) were acute, and 1298 ($86.5 \pm 1.7\%$) had a chronic ulcer. In 149 ($16.7 \pm 1.3\%$) retrospectively analyzed patients, an acute ulcer was observed, and in 742 ($83.3 \pm 1.3\%$) there was a chronic ulcer. Of the prospectively analyzed 610 patients, 54 ($8.9 \pm 1.2\%$) were diagnosed acute, and 556 ($91.2 \pm 1.2\%$) had a chronic ulcer.

On the basis of anamnestic data admitted to the clinic with a diagnosis of AGDUB in 638 ($42.5 \pm 1.3\%$) patients, primary was detected, in 863 ($57.5 \pm 1.3\%$) - secondary bleeding.

Of the 1501 patients with bleeding, 17 ($1.1 \pm 0.3\%$) had perforation, 29 (1.9 ± 0.4) - penetration and 56 ($3.7 \pm 0.5\%$) - stenosis.

The severity of hospitalized patients was assessed using the SAPS (Symplified Acute Physiological Score) scale.

The scores on SAPS scale were 5-8 in 402 ($26.8 \pm 1.1\%$) patients (retrospective - 217, prospective 185), 9-12 in 385 ($26.7 \pm 1.1\%$) patients (retrospective 229, prospective 156), 13-16 in 584 ($38.9 \pm 1.3\%$) patients (retrospective 373, prospective 211), 17-20 in 80 ($5.3 \pm 0.6\%$) patients (retrospective - 43, prospective - 37), and ≥ 21 in 50 ($3.3 \pm 0, 5\%$) patients (retrospective - 29, prospective - 21).

In general, 357 ($23.8 \pm 1.1\%$) patients had various concomitant somatic diseases: in 219 ($24.6 \pm 1.4\%$) retrospectively and in 138 ($22.6 \pm 1.7\%$) prospectively analyzed patients. With the characteristic of concomitant diseases, ischemic heart disease ($7.1 \pm 0.7\%$), hypertension of II - III stage ($5.4 \pm 0.6\%$), diabetes mellitus ($3.1 \pm 0.4\%$) were most often detected and alcoholic cardiomyopathy ($2.6 \pm 0.4\%$).

Of the 610 prospectively analyzed patients who received con-

servative and surgical treatment in 360 patients, studies were conducted with a view to comparatively studying the correcting effect of Betaleikin to immune status and cytokine profile (in 170 patients) and cord blood progenitor cells (in 10 patients), as well as Mexidol as an antioxidant (in 170 patients). In accordance with the goal and objectives, the patients were divided into two groups - comparative and main. Of the 180 patients in the comparative group (I group), 123 patients (Ia subgroup) received standard standard conservative therapy. The Ib subgroup of the comparative group included 57 patients who received traditional basic intensive therapy in the postoperative period.

180 patients of the main group (group II) were also divided into three subgroups. 107 patients of the IIa subgroup with standard conservative therapy were treated with systemic cytokine therapy (SST) with Betaleukin and antioxidant therapy with 5% mexidol.

In the postoperative period, 63 operated patients of subgroup IIb, on the background of traditional basic therapy, were performed immunocorrection with Betaleukin and antioxidant therapy with Mexidol.

In patients of the main group, SCR was performed taking into account contraindications, and at the same time, Betaleukin was prescribed according to the depth of the secondary immunodeficiency and the severity of blood loss. On the background of immunostimulation with Betaleukin, the duration of antioxidant therapy and the dose of Mexidol were selected taking into account the intensity of lipid peroxidation processes and the volume of blood loss:

- in case of mild blood loss - Betaleukin at a dose of 0.5 μg intravenously in 500 ml of saline solution 1 time per day, only 3 days + in 150 ml of saline solution 2.0 ml 5% Mexidol 1 time per day, only 3 days

- in case of moderate blood loss - Betaleukin in a dose of 1 μg intravenously in 500 ml of saline solution 1 time per day, only 3 days + in 150 ml of saline solution 2.0 ml of 5% Mexidol 2 times a day, only 5 days

- in case of severe blood loss - Betaleukin in a dose of 1 μg intravenously in 500 ml of saline solution 1 time per day, only 5 days +

in 150 ml of saline solution 2.0 ml 5% Mexidol 2 times a day, only 7 days.

The IIc subgroup of the main group included 10 patients with severe blood loss, who in the postoperative period were intravenously administered with progenitor cord blood stem cells (CC) in an amount of $20 \cdot 10^6$ cells.

Fibrogastroduodenoscopy (FEGDS) was performed for all patients admitted to the clinic during the first hours. For the treatment, different methods of endoscopic haemostasis - injection, diathermo-coagulation, clipping.

Basically, to achieve the endoscopic hemostatic effect, combined methods were used: injection + diathermocoagulation, injection + argon plasma coagulation, injection + ACC, clips overlay + injection. An endoscopic study of patients admitted to the clinic was conducted on the background of conservative therapy: infusion-transfusion, general hemostatic, antisecretory, anti-helicobacter and restorative. When infusion-transfusion therapy was taken into account the stability of hemostasis, the severity of blood loss and hypovolemia, the depth of hemodynamic changes, the age of patients and related pathologies.

For anti-ulcer treatment, antisecretory drugs and proton pump inhibitors (PPIs) were used. For the purpose of antisecretory therapy, one of the H2 histamine blockers was administered intravenously. PPI and antisecretory drugs were intravenously injected for 5-7 days, then switched to tablet form.

Of the prospectively investigated in 156 patients by the express method, using the urease test ("kampi-test"), the level of infection of the gastric mucosa and duodenum *H.pylori* was studied. Of the 156 patients with AGDUB in 102 ($65.4 \pm 3.8\%$), *H.pylori* was detected: in a significant amount (++++) in 52, in a moderate amount (++) in the 31 and in an insignificant - weak dissemination (+) was detected in 19 patients. In 54 ($34.6 \pm 3.8\%$) cases, *H. pylori* was not detected.

H. pylori positive patients after stabilization of the condition against the background of complex treatment was carried out anti-helicobacter treatment. The efficacy of *H. pylori* eradication was evaluated after 30 days of treatment.

Therapeutic endoscopy and general hemostatic therapy in 7 patients was ineffective and bleeding continued. Of the 1494 patients in whom hemostasis was achieved, in 122 patients recurrence of bleeding occurred: 51 in the first 24 hours after admission to hospital, in 48 cases after 24-48 hours and in 23 patients after 48 hours.

With continued and recurrent gastroduodenal bleeding, as well as in cases of high risk of recurrence and other indications, various surgical operations were performed on 275 patients (Table 1).

Table 1

The distribution of surgical interventions by urgency

Urgency of operation	Clinical and endoscopic indications for surgery	Total number of patients			In total
		GU	DU	GDU	
Emergency	1. Continuing bleeding 2. Perforation 3. Recurrent bleeding 4. High risk of bleeding recurrence	11	70	7	88 32,0±2,8%
Urgent	1. High risk of bleeding recurrence 2. Recurrence of bleeding	13	56	9	78 28,4±2,7%
Delayed	1. Real danger of relapse on the background of unstable hemodynamics 2. Penetrating and large chronic ulcer 3. Stenosis of the output section of the stomach	19	35	4	58 21,1±2,5%
Early planned	1. Chronic kaleznaya ulcer 2. Repeated ineffective conservative therapy 3. Suspicion of malignancy	11	23	17	51 18,6±2,3%
Total		54	184	37	275 100%

The volume and nature of surgical interventions in patients is presented in table 2. As follows from table 2, 56 patients (20.4% ± 2.4%) underwent radical surgery — gastric resection in various modifications (Table 2).

Conditionally radical excision of the ulcer in combination with stem vagotomy and pyloroplasty was performed in 105 patients (38.2

$\pm 2.9\%$), excision of the ulcer and pyloroplasty were performed in 99 patients ($36.0 \pm 2.9\%$). Palliative surgery — suturing the ulcer was performed in only 15 patients ($5.5 \pm 1.4\%$).

Table 2

The scope and nature of surgical operations

Surgical operations	Groups		Total (n=275)
	Retrospective (n=145)	Prospective (n=130)	
Excision of an ulcer + pyloroplasty	99	–	99
Excision of an ulcer + pyloroplasty	9	10	19
Resection of the stomach according to Billroth II in various modifications	26	11	37
Excision of the ulcer + vagotomy + pyloroplasty	–	105	105
Closure of bleeding ulcer	11	4	15

With conservative therapy and surgical treatment in patients on admission, on the 3rd, 7th, 17th day of treatment in the peripheral blood, the content of CD3 +, CD4 +, CD8 +, CD19 + - lymphocytes was determined using the immunofluorescent method by specific binding of monoclonal antibodies to the corresponding immunocomponent cell antigens. Calculated immunoregulatory index (IRI) - the ratio of CD4 + / CD8 +.

The content of serum IgA, IgM, IgG and circulating immune complexes (CIC) was determined, the phagocytic activity of neutrophilic granulocytes was assessed by determining the phagocytic index (PI) and phagocytic number (PN). Also studied the activity of lysozyme in the gastric, and the concentration of IgA, M, G - in the duodenal contents. The concentration of proinflammatory (TNF α , IFN γ , IL-1, IL-2, IL-6, IL8) and anti-inflammatory (IL-4, IL-10) cytokines was also determined in the blood using ELISA using Protein Contour Reagent Kits. (St. Petersburg). The ratio of TNF α / IL-10 and IL-2 / IL-4 was also studied.

The content of IL-6 in the gastric contents was determined at admission, and in the urine - in the dynamics during treatment.

In both conservatively treated and operated patients, on admission for 1-3, 5-7, 10-14 days of treatment, the state of lipid peroxidation processes was judged by studying the content of diene conjugates (DC), malonic dialdehyde (MDA) in plasma, reduced glutathione (GSH), glutathione peroxidase (GP) in erythrocytes and total antioxidant activity (TAA) in erythrocytes using known methods described in the literature (AM Goryachkovsky, 1998). The content of DC and MDA in biopsy specimens taken from the edges of the ulcer was also determined. To assess the level of endogenous intoxication in plasma, the content of medium-molecular peptides (MMP) in the blood was studied in dynamics (VV Nikolaichuk et al., 1991).

For the most reliable prediction of the risk of recurrence of bleeding (RC) based on the theories of fuzzy logic Lutvi Zadeh in scientific cooperation, the Research Institute of Applied Mathematics of Baku State University has developed and implemented a fuzzy module in the clinic. In order to reliably identify the RK using fuzzy logic, the MATLAB TOOLBOX software package was used.

The obtained digital data was processed by the methods of variation (Wilcoxon's nonparametric method – Mann-Whitney), the correlation method (the linear correlation coefficient with the Fisher's Z-transform) and the discriminant one – odds ratio (OR) with a 95% confidence interval (DI) analysis.

RESULTS OF THE OWN RESEARCH

The obtained data showed that in AGDUB, both in the cellular and humoral immunity, statistically significant changes of the stress type occur. This shows the reduction of CD4 + potential, CD4 + / CD8 + ratio and phagocytic activity of neutrophils. CD19 +, lymphocytes and CIC contents. In these patients, they are characterized by dysimmunoglobulinemia.

So, when compared with the norm, a statistically significant decrease in the number of CD3 + by 32.9%, CD4 + - 32.5%, CD8 + - 13.3%, CD4 + / CD8 + - 23.2%, FI - 18.9% , IgA - 16.5%, IgM - 15.8% and IgG - 10.7%. On the contrary, in these patients the number of CD19 + - lymphocytes by 58.8% (p <0.001), PN - 58.8% (p

<0.001) and the CIC 2.3 times ($p < 0.001$) exceeds the norm.

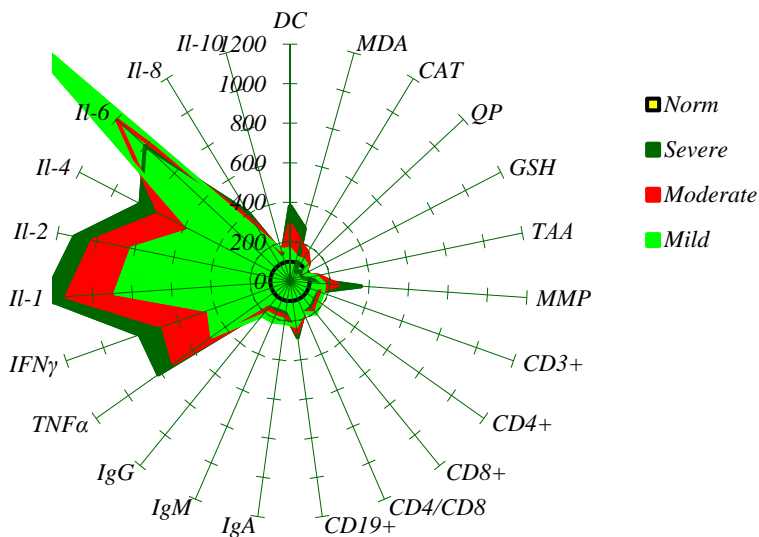
The activity of lysozyme in the gastric juice is reduced by 38.3% ($p < 0.001$) compared to the norm. Also in the duodenal contents, the concentrations of IgA, M and G, respectively, were reduced by 72.0% ($p < 0.001$), 55.1% ($p < 0.001$) and 37.6% ($p < 0.001$) compared to the norm.

Upon admission to the clinic in patients with cytokine status, a deep imbalance was also detected. Thus, when compared with the norm, a statistically significant increase in the level of pro-inflammatory cytokines was detected (TNF α - by 5.7 times, IFN γ - by 5.4 times, IL-1 - by 9.9 times, IL-2 - by 8.7 times, IL-6 by 12.8 times, IL-8 by 2.5 times), as well as the level of anti-inflammatory cytokine IL-4 by 6.2 times ($p < 0.001$) and vice versa, the decrease in the content of IL-10 is 45.2% ($p < 0.001$). Despite the fact that the level of IL-6 in the urine is 8.2 times higher, the level of this cytokine in gastric juice is 37.5% less than the norm ($p < 0.001$). When compared with the norm, the imbalance of systemic cytokine profile parameters led to an increase in the index of TNF α / IL-10 ratios 11.7 times ($p < 0.001$), and the ratio index of IL-2 / IL-4 by 53.3% ($p < 0.001$).

In patients with admission to the POL-AOD system, profound changes are also observed: an increase in the concentration of DC by 2.8 times ($p < 0.001$), MDA by 2.0 times ($p < 0.001$), CAT by 17.8% , in GP erythrocytes by 8.4% and total antioxidant activity of AAA by 17.1%, and vice versa, a decrease in the concentration of reduced glutathione QSH by 25.0% ($p < 0.001$). Against this background, an increase by 2.6 times ($p < 0.001$) in the level of a marker of endogenous intoxication - medium molecular peptides (MMP) (figure 1) is detected compared with the norm. In biopsy specimens taken from the edges of a bleeding gastric ulcer, the DC content is 2.2 times ($p < 0.001$), and the MDA content is 3.1 times ($p < 0.001$) more than normal. In biopsy specimens taken from the edges of a bleeding duodenal ulcer, the level of DC and MDA exceeds the norm by 89.3%, respectively ($p < 0.001$) and 2.9 times ($p < 0.001$).

However, the depth of changes in immune status, cytokine profile, and LP processes directly depends on the severity of the bleed-

ing: the depth of changes increases as the volume of lost blood increases (Graph 1). Comparative dynamic study of EI's, immune, cytokine profile and indicators of LP processes in patients involved in prospective studies demonstrated that introduction of betaine and mexidol into the basic treatment complex showed their efficiency.



Graph 1. Changes in cytokines, immune indicators and antioxidant system in blood, depending on the degree of blood loss.

Practically, in the Ia subgroup, there is a tendency toward normalization of cell immunity in dynamics on the background of traditional conservative treatment in all severity levels. However, the dynamics of change in the immune indicators learned depend on the severity of the bleeding.

The amount of CD3+ - lymphocytes which in the slight bleeding was lower than normal by 21.1% ($p < 0.001$), 30.5% in moderate severe cases ($p < 0.001$) and 43.7% in severe cases ($p < 0.001$). On the 14th day of the observation these parameters reached the level of 15.9%, 24.0% and 28.8% respectively.

Similar analogs are noted in the dynamics of immunological in-

dicators such as CD4 +, CD4 + / CD8 + and phagocytic index. In all severities of bleedeng despite CD19 + - higher lymphocyte levels diminished on the background of conservative therapy but remain high at the end of treatment, and dysimmunoglobulinemia persists.

The introduction of betaine in traditional conservative therapies normalizes the amount of CD3 + CD4 + in patients with mild to severe dyspnoea, while at the same time significantly reducing the CD8 + concentration in the operating cycle to the nearest norm. It should be noted that cytokine therapy with betaine has a positive effect on humoral immune system. Thus, the number of CD19 + lymphocytes, which is 29.9% higher than the norm ($p < 0.01$) in patients with mild to moderate degree, is approaching to norm at the end of treatment. In these patients, IgA, IgM and IgG levels are significantly lower than those of healthy individuals.

In patients moderate blood loss, CD19 + is significantly reduced by 16.5% less than the Ia subgroup at the end of treatment. In moderate blood loss, all three immunoglobulin concentrations are rapidly increased due to treatment, and approach to norm unlike the Ia subgroup.

In patients with severe bleeding on admission the CD19 + lymphocytes in the norm being 77.5% ($p < 0.001$) more - $22.7 \pm 1.2\%$, after entering betaleukin to complex treatment, comparing to initial level, its concentration decreased by 27.5% and was $16.4 \pm 0.9\%$ ($p < 0.001$). However, CD19 + in patients with similar severity and undergoing basic conservative therapy is about $19 \pm 1.2\%$ at the end of the treatment. It should be noted that IgA concentration, which is statistically accurate to 36.8% less than normal, increases rapidly in the patients at the rate of 16.5% higher than in the Ia subgroup at the end of the observation, while entering the clinic due to the introduction of beta-cure into a major therapeutic therapeutic complex. At the same time, on the background of a complex baseline and cytokine therapy with betaleukine in patients with severe blood loss can be reached statistically significant 35.7% IgM concentration in the blood compared to healthy individuals, with a rate of 12.8% less than normal at the end of treatment. However, IgM concentration in the Ia subgroup is statistically 35.9% less than normal.

A comparative assessment of changing IgG in dynamics in severe blood loss showed better results in the IIa subgroup. IgG concentration, which is significantly lower than norm in patients with both subgroups, start to increase from third consecutive day in dynamics. At the end of treatment, this increase was statistically inaccurate 10.7% in the Ia subgroup and 29.3% in the IIa subgroup ($p_0 < 0.01$), IgG levels in the IIa subgroup were statistically inaccurate 12.9% higher than the Ia subgroup reaching the limit.

Traditional basic conservative therapy has a negative effect on cytokine imbalance. Thus, in the background of traditional conservative therapy, decreased IL-1 production on the background of increased secretion of inflammatory cytokines such as $TNF\alpha$, $IFN\gamma$, IL-2, IL-6, IL-8 in patients with mild blood loss in Ia subgroup production of IL-1 decreased and increasing of synthesis of antiinflammatory cytokines such as IL-4 and IL-10 were observed.

There is a gradual decline in $TNF\alpha$, $IFN\gamma$, IL-1, IL-6, IL-8, IL-10 levels in further periods, but increase in IL-2 and IL-4 synthesis was observed. At the end of the observation in comparison with previous levels the $TNF\alpha / IL-10$ ratio was 40.0% ($p_0 < 0.001$) and IL-2 / IL-4 ratio was 60.0% ($p_0 < 0.001$). In patients with moderate blood loss, the decreasing in $IFN\gamma$ levels and the the increase in other cytokine levels in the first 3 days are due to traditional conservative therapy. There is a significant decrease in all IL-4 cytokines and IL-4 on the 14th day, but increasing IL-10 levels. On the 14th day of the treatment, patients with Ia subgroup with severe blood loss were statistically accurate $TNF\alpha$ - 5.6 times, $IFN\gamma$ - 7.0 times, IL-1 - 9.2 times, IL-2 and IL-4 - 15.3 times The concentration of IL-10 reaches 10.5 ± 1.4 pg / ml (norm - 14.2 ± 1.2 pg / ml).

In the IIa subgroup, there is a full range of cellular immunity and LPO-AOD system symptoms, normalize MMP levels, and humoral immune parameters and cytokines levels. Moderate and severe blood loss accelerate the elimination of suppression state, cytokine imbalance and lipoperoxidation disorders in both rings of immunity, compared to Ia subgroup 28.5% ($p_1 < 0.001$) and 27.2% ($p_1 < 0.001$), respectively

Comparing of CD3 + - lymphocytes by 22.3%, CD4 + - 18.6%

and CD8 + - 8.6% to normal parameters preoperatively in patients who underwent surgical interventions in the Ib subgroup of mild bleeding and had a traditional baseline therapy postoperatively at a slower rate to the norm. At the end of the study, CD3 + was found to be 20.0% ($p < 0.001$), CD4 + 17% ($p < 0.01$) lower, and CD8 + 18.1% ($p < 0.01$) higher. The level of PhI is lower than 12.7% ($p < 0.01$) before the surgical intervention can not be normalized as it is gradually increasing after the postoperative period. In these patients, the IgA was significantly higher in the postoperative period compared to the norm by 15.0%, IgM - 21.0%, IgG - 27.6% ($p < 0.001$) and CIC 46.3% ($p < 0.001$) relatively minimal change. The TNF α level was 3.9 times statistically significant, IFN γ - 3.2 times, IL-1 - 7.9 times, IL-2 - 7.2 times, IL-6 - 19.0 times in comparison to healthy individuals. IL-8 is 81.7% higher, and the concentration of this anti-inflammatory cytokines in the blood increases for the first 3 days after surgery, but then decreases. On the 14th day of treatment, TNF α was 3.9 times higher than norm ($p < 0.001$), IFN γ - 3.0 times ($p < 0.001$), IL-1 - 4.3 times ($p < 0.001$), IL-2 - 12, 1 time ($p < 0.001$), IL-6 - 12.0 times ($p < 0.001$) and IL-8-69.3% ($p < 0.01$). The inflammatory cytokine IL-4, which was 4.6 times higher than norm ($p < 0.001$) during the operation period, increased in the post-operative period and reached the maximum in 14 days - 27.5 times higher than norm ($p < 0.001$). In preoperative period, the IL-10 inflammatory cytokine IL-10, which was 33.3% ($p < 0.05$) less than the norm, was normalized to 14 days, increasing by 48.8% ($p < 0.05$) compared to the initial one. The IL-6 concentration in the urine before the intervention was 5.8 ($p < 0.001$) times higher than the norm and gradually declined after the postoperative period but remained at the end of the study at 4.5 times more than the norm ($p < 0.001$).

In these patients, LPO-AOD indicators, which are high in the treatment period, start to normalize to the postoperative 3-day therapy after a surgical intervention. However, at the end of treatment, the amount of DK in plasma was 18.6% ($p < 0.01$), MDA - 9.2% ($p < 0.01$), CAT - 10.9%, APh in erythrocyte - 10.3%, GAA - 13.9% ($p < 0.001$) remains high, but GSH (reduced glutathione) was normalized. MMP (medium molecular peptides) levels in plasma were

higher by 90.1% ($p < 0.001$) than the normal range, but decreased after surgical intervention, and this decrease was 31.3%, but remains 30.5% higher than norm ($p < 0.001$).

In surgical treatment of patients with mild bleeding in postoperative period of SCT with betaleukine and AT with 5% mexidol compared to the initial parameters CD3 + - lymphocytes was increased by 26.9% ($p_0 < 0.001$), CD4 + by 15.2% ($p_0 < 0.05$), CD4 + / CD8 + ratio by 22.2% ($p_0 < 0.001$), PhI - by 13.7% ($p_0 < 0.01$), reducing increased levels of CD19 + lymphocytes and immunoglobulins. Compared with similar patients in the Ib subgroup, CD19 + - lymphocytes are reduced by 16.9% ($p_1 < 0.05$) and CIC levels by 22.5% ($p_1 < 0.01$). Also, the TNF α concentration in the blood at the end of treatment was 46.6% ($p_1 < 0.01$), IFN γ - 42.2% ($p_1 < 0.01$), IL-1 - 56.6% ($p_1 < 0$) compared to the Ib subgroup patients. 0.001), IL-1 - 64.4% ($p_1 < 0.001$), IL-4 - 66.6% ($p_1 < 0.001$), IL-6 - 60.0% ($p_1 < 0.001$), IL-8 - 24. , Less than 1%, and IL-10 levels are fully normalized. In urine, IL-6 levels are 49.9% ($p_1 < 0.01$) lower than those in the Ib subgroup on the 14th day of the postoperative day.

In patients with mild bleeding, injection of 5% mexidol in combination with betaleukine into basic complex therapy after surgical intervention has an inhibitory effect on lipoperoxidation processes. Thus, by the end of the study, the amount of MDA in plasma, GSH in erythrocytes is fully normalized, and the DC, KAT, APH, and GAA are approaching normal levels. MMP in plasma is 17.9% ($p_1 < 0.01$) lower than the same indicator in the Ib subgroup.

Patients with moderate bleeding in the Ib subgroup had a mean CD3 + ratio of 31.3% ($p < 0.001$), CD4 + - 37.2% ($p < 0.001$), CD8 + - 18.2% ($p < 0.001$), CD4 + / CD8 + - 19, 4% ($p < 0.001$), PhI - 17.5% ($p < 0.001$), IgA - 25.9% ($p < 0.001$), IgM - 22.0% ($p < 0.05$), IgG - 25 , 4% ($p < 0.001$), on the contrary, CD19 + - 63.9% ($p < 0.001$), CIC - 2.2 times ($p < 0.001$), and PhI - 62.8% more than the baseline therapy has a very weak effect on the change in the positive direction. Thus, the level of these indicators does not differ significantly from baseline in the 14th day of treatment. At the end of observation, TNF α content was 14.5%, IFN-gamma, - 39.8%, IL-1 - 31.3% ($p_0 < 0.05$), IL-6 - 14.1%, IL-8 - 24, compared with baseline. This indicates that

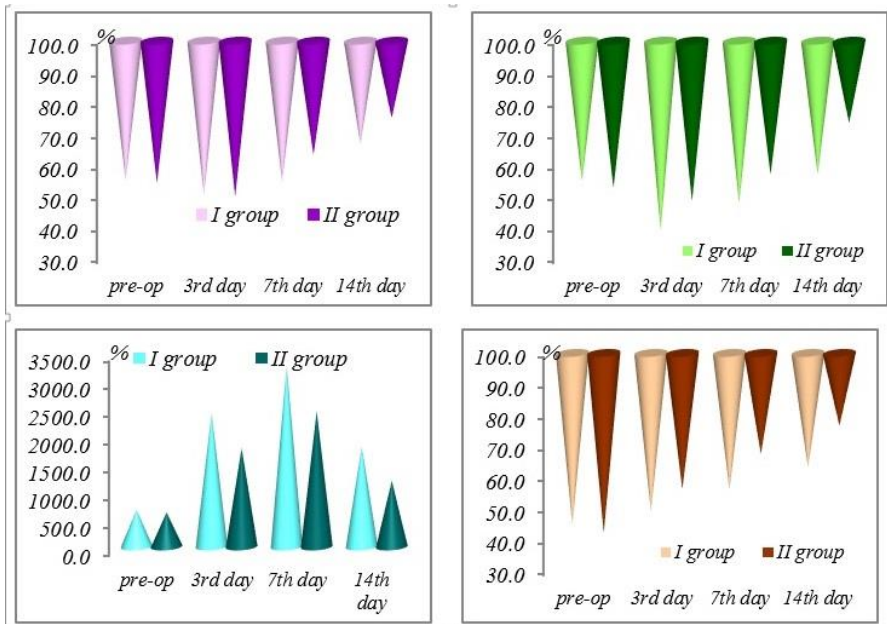
cytokine imbalance continues. By the end of the study, the level of DC in plasma was 52.9% ($p_0 < 0.001$), MDA - 46.3% ($p_0 < 0.001$), KAT - 18.8%, MMP 23.2% ($p_0 < 0.05$), erythrocytes. APh remains 12.8% ($p_0 < 0.001$), GSH - 16.2% ($p_0 < 0.01$).

At the end of the study, CD3 + - lymphocytes were 16.0% ($p_1 < 0.05$), CD4 + - 22.6% ($p_1 < 0.01$) compared with similar IB subgroups in patients with moderate bleeding in the subgroup IIb who underwent SST and AT after surgical intervention. , 01), CD8 + - 10.5% ($p_1 < 0.05$), CD4 + / CD8 + - 12.7%, IgA - 9.8%, IgM - 11.0%, IgG - 13.5% ($p_1 < 0.05$), FA is more than 9.2%, but CD19 + is 21.8% ($p_1 < 0.05$), DIC is 27.0% ($p_1 < 0.01$), FA is less than 5.3%. . Also, in these patients, the TNF 34 concentration was 34.4% ($p_1 < 0.05$), IFN Ib - 26.4%, IL-1 - 50.0% ($p_1 < 0.001$), IL-2 in the 14th day of treatment compared with Ib group. - 57.8% ($p_1 < 0.001$), IL-4 - 33.5%, IL-6 - 35.4%, IL-8 - 34.9% ($p_1 < 0.05$) less, IL-10 Increase by 30.7%, and the elimination of cytokine imbalance is significantly accelerated. Compared with the baseline for this period, the level of DC in plasma was 59.9% ($p_0 < 0.001$), MDA - 48.7% ($p_0 < 0.001$), KAT - 30.0% ($p_0 < 0.001$), MMP - 43.8%. $p_0 < 0.001$), APh - 20.5% ($p_0 < 0.001$), in erythrocytes, UAA - less than 22.5% ($p_0 < 0.001$), but GSH – was 16.8% ($p_0 < 0.01$) higher.

Deep immunosuppression rates in patients admitted to the clinic with severe bleeding in the subgroup Ib compared with the norm is statistically valuable for CD3 + - lymphocytes 45.1%, CD4 + - 45.7%, CD8 + - 32.7%, CD4 + / CD8 + 20.2%, IgA - 37.1%, IgM - 44.9%, IgG - 30.4%, PhI - 25.9% less, but CD19 + - 88.4%, CIC - 3.1 times higher and PhI - 75.4% shows itself. Traditional conservative therapy following surgical intervention has focused on the normalization of both indicators of the immune system from the early postoperative period in the dynamics. However, on the 14th day of observation, CD3 + had a statistical accuracy of 33.6%, CD4 + - 40.8%, CD8 + - 30.3%, CD4 + / CD8 + - 16.0%, IgA - 33.4%, IgM - 42.8. %, IgG - 30.3%, PhI - 20.3% less, but CD19 + - 75.8%, CIC - 2.5 times, and PhA - 49.9%, ie deep immunosuppression continues. Deep cytokine imbalance also continues during this period, as the concentration of TNF α in the blood serum is 6.4 times ($p < 0.001$),

IFN γ - 4.4 times ($p < 0.001$), IL-1 - 10.5 times ($p < 0.001$), IL-2 - 12.7 times ($p < 0.001$), IL-4 - 19.0 times, IL-6 - 11.3 times, IL-8 - 2.5 times and IL-10 - less than 36.3% ($p < 0.01$). By the end of treatment, the level of IL-6 in urine was 8.8 times ($p < 0.001$) more than normal, TNF α / IL-10 - 11.2 times ($p < 0.01$), and the IL-2 / IL-4 ratio was 34.3 % ($p < 0.001$) remains low.

In these patients, the amount of DC by the 14th day of the post-operative day compared with initial parameter decreased by 44.8% ($p_0 < 0.001$), MDA - by 33.9% ($p_0 < 0.001$), KAT by 47.5% ($p_0 < 0.01$)., GSH - 22.4% ($p_0 < 0.001$), APh - 54.7% ($p_0 < 0.001$), UAA - 25.8% ($p_0 < 0.001$), but no indicators can be normalized. During this period, the level of MMP in plasma is 35.4% ($p_0 < 0.001$) lower than the baseline, but remains 2.4 times higher ($p < 0.001$) than the norm (Graph 2).



Graph 2. Comparative assessment of changes in blood CD3 + - lymphocytes (left above) , IgM (right above), IL-4 (left below) and IL-10 (right below) levels in patients with surgical intervention in the context of severe bleeding (norm - 100%).

Patients who underwent surgical intervention in the IIB subgroup in background of bleeding compared to SST with betaleukine, the patients with a similar severity group in CD3 + was 12.3%, CD4 + - 27.6%, CD8 + - 11.9%, CD4 + / CD8 + 4%, IgA - 16.8%, IgM - 28.1%, IgG - 13.6%, PhI - 4.1% more, but CD19 + - 17.3%, CIC - 24.4% and PhA - 14,8% were less. Also, during the same period, the concentration of TNF α in the blood was 38.3%, IFN γ - 31.2%, IL-1 - 43.2%, IL-2 - 42.8%, IL-4 - 32.3%, compared with similar indicators of subgroup Ib, IL-6 - 36.4%, IL-8 - 33.2% less, IL-10 - 20.2%. In urine, the amount of IL-6 is 59.6% ($p_1 < 0.001$) lower than that in the Ib subgroup, the TNF α / IL-10 ratio is 54.0%, and the IL-2 / IL-4 ratio is 18.3%.

Due to the antihypoxant, antioxidant, and membranoprotective effects of mexidol at the end of treatment in these patients, the amount of DC in blood is 33.5%, MDA - 24.8%, APh - 12.4%, but not KAT - 8.7%, GSH - 6.9% and UAA - 7.3%. In the subgroup IIB patients, the amount of MMP in plasma during this period was 0.96 ± 0.10 g / l, which is 23.1% ($p_1 < 0.05$) lower than the same level in the Ib subgroup.

In 10 patients of the IIC subgroup with severe acute blood loss, the blood loss the day after surgery, against the background of generally accepted comprehensive basic therapy, 20×10^6 cells of regenerative stem cells (SC) were injected intravenously.

On the 5th day after SC transfer (7th day after surgery) CD3 + - lymphocytes increased by 73.8% ($p_0 < 0.001$), CD4 + - 2.0 times ($p_0 < 0.001$), CD19 + - 40.0 % ($p_0 < 0.001$), CIC is less than 62.6% ($p_0 < 0.001$). The concentration of IgA, IgM and IgG is approaching the norm. During this period, the level of IFN γ in the blood decreased to 76.9% ($p_0 < 0.001$), IL-1 to 80.5% ($p_0 < 0.001$), IL-2 to 69.6% ($p_0 < 0.001$), but not IL. -10 approaches the norm by 2.1 times ($p_0 < 0.01$) more than the baseline. At the same time, the dynamics of hemoglobin volume and erythrocyte volume increase in these patients are significantly accelerated.

Out of 1501 patients, 452 ($30.1 \pm 1.2\%$) endoscopic hemostasis was performed in the clinic: F Ia, b, cases with F, I, b, and prophylactic in F IIA, b, c. Of the 452 patients, 245 were included in the retro-

spective and 207 prospective groups. Out of these 452 patients, endochemostasis was performed in 107 of the gastric ulcer and in 345 of bleeding oncology. Endoscopic hemostasis methods were selected based on the intensity of bleeding. Thus, most of the 183 patients with F Ia and F Ib with intensive bleeding were used in 70 - 70 injections. F IIa, F IIb, and F IIc were given preferential injection in separate hemostasis during intravenous bleeding. A total of 452 endoscopic hemostasis patients were used in 37 applications, 29 injections, 61 plasma coagulation, 51 diathermocoagulation, 28 ligature and clip insertion, and 146 patients using combined methods. Of the 306 patients who underwent endoscopic hemostasis with separate methods, 35 ($11.4 \pm 1.8\%$) had recurrent hemorrhage in 1 to 10 days in 14 ($14.0 \pm 2.6\%$) of 146 patients. It should be noted that F Ia and F Ib were the highest number of bleeding residues after endoscopic hemostasis. It is also interesting to note that there is a direct relationship between the size of the bleeding residue and the localization and size of the ulcer. Of the 245 patients retrospectively analyzed, 44 ($18.0 \pm 2.5\%$) were recurrent, and 7 ($3.4 \pm 2.3\%$) out of 207 patients included in the prospective analysis (3 - baseline and 4 - in the comparison group). Overall, therapeutic and preventive endoscopic hemostasis yielded positive results in 409 patients ($90.5 \pm 1.4\%$). Thus, 7 of 1501 patients did not have endochemostasis, 20 had residual bleeding after therapeutic endoscopic hemostasis and 31 after prophylactic endochemostasis. In F + II intravenous hemorrhages without prior prophylactic endochemostasis and conservative therapy, 71 patients had such complication. In total, 1501 patients had recurrent bleeding in 122 ($8.1 \pm 0.7\%$) within 1 to 10 days of hospital stay.

Out of 1501 patients, 1226 patients ($81.7\% \pm 1.0\%$) underwent comprehensive conservative therapy: retrospective - 746 ($60.8 \pm 1.4\%$) and prospective - 480 ($39.2 \pm 1.4\%$). Thus, of the retrospective analyzes of 891 patients who received treatment on the basis of individual active tactics, 746 patients received conservative therapy and 145 had surgery. In 891 patients, 83 ($9.3 \pm 1.0\%$) had inpatient hemorrhage, and in 23 of these patients endoscopic hemostasis and hemostatic therapy were ineffective and urgent surgical intervention

was performed. Out of 145 patients, 67 were urgent, 35 were urgent, 29 were delayed and 14 were operated early. In these patients, 35 (24.1 ± 3.6%) were radical, 99 (68.3 ± 3.9%) had conventional radical and 11 (7.6 ± 2.2%) palliative operations. executed. In the retrospective group, total lethality was 8.3 ± 0.9% (74 patients), postoperative lethality was 7.5 ± 0.96% (56 patients), and postoperative lethality was 12.4 ± 2.7% (18 patients). . In 41 patients (28.3 ± 3.7%), there were various complications after surgery.

Within the prospectively analyzed 610 patients, individualized treatment tactics were followed by conservative therapy in 480 patients (78.7 ± 1.7%) and surgical intervention in 130 (21.3 ± 1.7%). In the prospective group, 350 patients had recurrent hemorrhage risk, based on a fuzzy module method developed by Lutfi Zade's fuzzy logic theory. For this purpose, in accordance with the phase logic output scheme, RF fuzzy input variables affecting the risk of gastroduodenal hemorrhage and term sets for output modifications are specified:

X1: According to "Forrest": {"acute" 1-3; "moderate" 2-5; "mild" 4-6}

X2: "The diameter of the ulcer": {"small" 0-1.5; "Average" 0.5-2.5; "Big" 1,5-3}

X3: "Localization" of the incoming variable: {"very dangerous" 1-1,6; "Little dangerous" 1.4-2}

X4: "Degree of blood loss" input variable: {"low" 0-0.4; "Average" 0.2-0.8; "High" 0.6-1}

X5: "Duration of illness": {"short" 0-1; "Average" 0.5-2.5; "Long" 2-3}

X6: "History of bleeding": {"yes" 0-0.6; "No" 0.4-1}

X7: "SAPS": {"low" 0-10 "medium" 5-20; "High" 15-25}

X8: Content of "IL-6 in gastric juice": {"low" 0-2.5; "Average" 2-3.7; "High" 3.3-4}

X9: Content of "IgA in duodenal juice": {"low" 0-3; "Average" 2.5-4.5; "High" 4-5}.

Y: - "Relapse" {"is" 0-0.6; "No" 0.4-1}

The input and output variables are introduced into the model using the MATLAB TOOLBOX software package under the FUZZY

LOGIC system.

If the result of the logical conclusion is higher than 0.5, the probability of relapse is large, if lower than 0.5, then the probability of relapse is low, if it is 0.5 or approaches 0.5, then it will be considered suspicious (maybe it may not be) For example, the result of inference will be $y = 0.769$ when evaluating the input variables $x_1 = 1$, $x_2 = 3$, $x_3 = 1$, $x_4 = 1$, $x_5 = 3$, $x_6 = 1$, $x_7 = 20$, $x_8 = 2$. Those. the probability of relapse is large (the maximum probability may be 1) (Fig. 1).

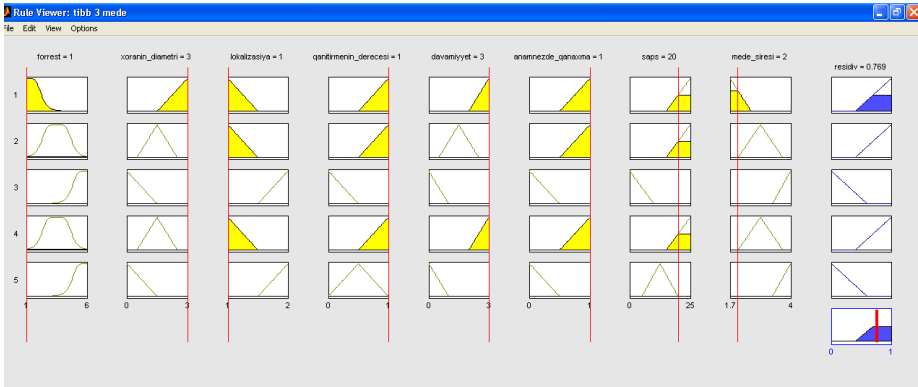


Fig. 1. The result of the logical conclusion $y = 0.769$ when evaluating the input variables $x_1 = 1$; $x_2 = 3$; $x_3 = 1$; $x_4 = 1$; $x_5 = 3$; $x_6 = 1$; $x_7 = 20$; $x_8 = 2$.

It also calculates the probability that each time the input of the input variables as a result of the built-in expert system will be extracted at the specific prices of the selected 8 indicators, that is, the BR for bleeding duodenal bleach. We evaluated the risk of recurrent bleeding in 350 patients admitted to the clinic with a diagnosis of malignant SCD using a fuzzy module. In 313 of 350 patients, the probability of recurrence (Y) was less than 0.5, 5 patients had $Y = 0.5$ and 32 had $Y > 0.5$. In all cases, the results were based on tactical choice and prevention of bleeding in high-risk patients. In 32 out of 350 patients, it was decided that the risk of recurrent hemorrhage was greater than 0.5. 25 patients underwent surgical intervention to pre-

vent bleeding, but 7 patients refused surgery. Seven patients who refused surgery had a bleeding relapse within 1 to 3 days, and they were operated urgently. Resuscitation of bleeding was suspected in 27 patients, and in 291, the likelihood of recurrent bleeding was low. However, 9 patients (7 - those with a residual probability and 2 with a low probability of recurrence) had recurrent hemorrhage. Thus, the prognosis was correct in 97.4% of cases with fuzzy module prediction. However, the prognosis for bleeding relapse by S. Kulbak's method is 88.0%.

Of the 130 patients in the prospective group who underwent surgical intervention, the surgical procedure was urgent in 21 patients ($16.2 \pm 3.2\%$), and in 38 ($29.2 \pm 4.0\%$) - emergency, 35 ($26.9 \pm 26\%$). 3.6%) and delayed in 36 ($27.7 \pm 3.9\%$). Out of 130 patients, 21 ($16.2 \pm 3.2\%$) were radical, 105 ($80.8 \pm 3.5\%$) had conventional radicals, and palliative interventions in 4 ($3.1 \pm 1.5\%$). executed. In the postoperative period, $15.4 \pm 3.2\%$ (20 patients) experienced various complications. In 610 prospective analyzes, total lethality was $4.8 \pm 0.9\%$ (29 patients): in 480 patients receiving conservative therapy - $4.6 \pm 0.9\%$ (22 patients) and 5.4 ± 130 in 130 patients who underwent surgery. 2.0% (7 people).

Comparative evaluation of STE with betaleukine and AT with 5% mexidol results during conservative and surgical treatment of AGIB was performed in 350 patients. Of the 123 patients who received standard complex conservative treatment in the Ia subgroup of the comparison group, 11 ($8.9 \pm 2.6\%$) deaths and 25 ($20.3 \pm 3.6\%$) complications were reported. In the II subgroup of the main group, complications were due to the inclusion of betalexin and 5% mecidol in a set of traditional baseline therapy measures in 11 patients ($10.3 \pm 2.9\%$) and death in 1 patient ($0.9 \pm 0.9\%$).

We have developed a consensus-based clinical practice algorithm of individual differential active treatment tactics, allowing patients to choose specific treatment tactics for each patient in the prospective group, taking into account endoscopic criteria for hemorrhage intensity and prognosis of the probability of RB (Figure 2).

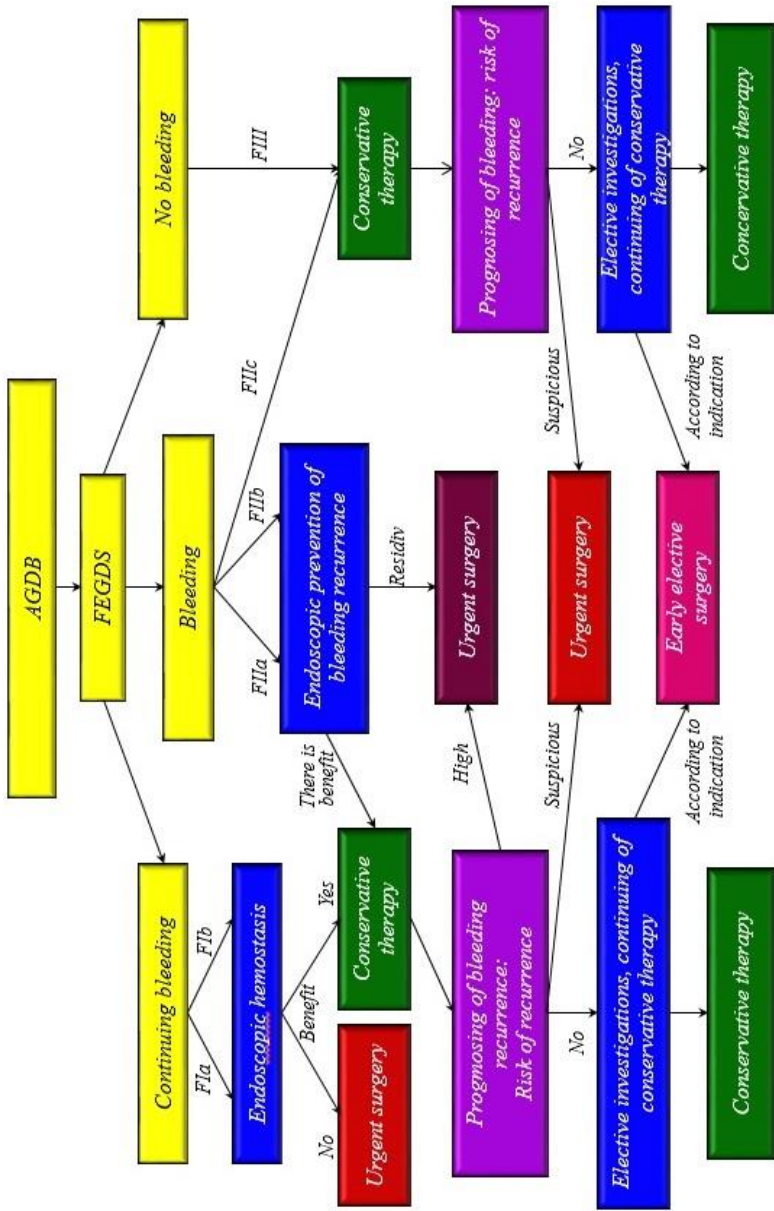


Fig.2. Algorithm for differentiated active therapeutic tactics in AGDB

Because of the direct relationship between the severity of bleeding, frequency of operations, and the percentage of mortality, the algorithm of choice of the volume of the operation developed by our patients based on the SAPS and ASA scale significantly improved the results of the procedure (Figure 3).

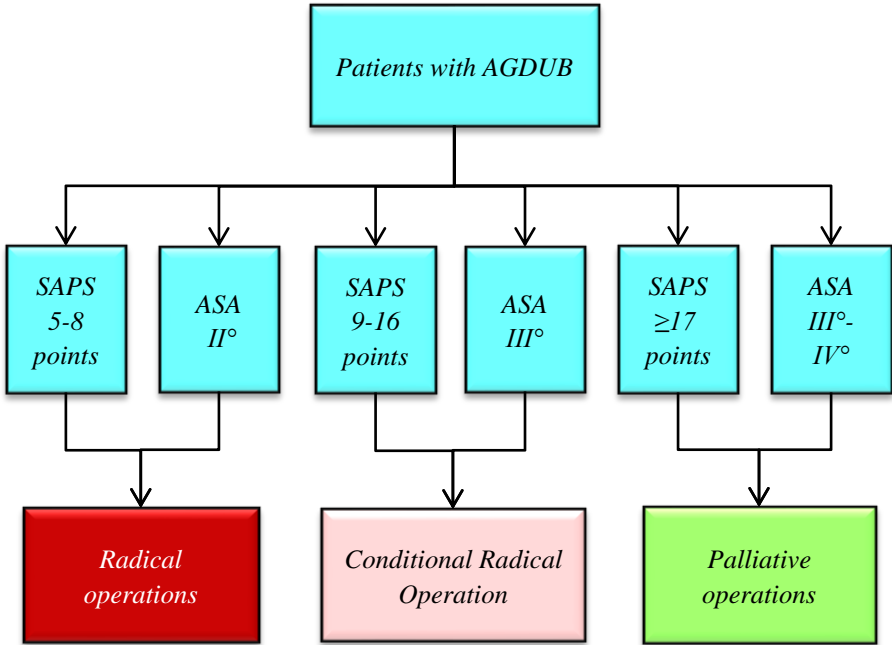


Fig. 3. The algorithm for selecting the volume of surgical operation based on SAPS and ASA scales.

25 patients underwent surgical intervention to prevent bleeding, but 7 patients refused surgery. Seven patients who refused surgery had a bleeding relapse within 1 to 3 days, and they were operated urgently. Resuscitation of bleeding was suspected in 27 patients, and in 291, the likelihood of recurrent bleeding was low. However, 9 patients (7 - those with a residual probability and 2 with a low probability of recurrence) had recurrent hemorrhage. Thus, the prognosis was correct in 97.4% of cases with fuzzy module prediction. However, the prognosis for bleeding relapse by S. Kulbak's method is

88.0%.

Of the 130 patients in the prospective group who underwent surgical intervention, the surgical procedure was urgent in 21 patients ($16.2 \pm 3.2\%$), and in 38 ($29.2 \pm 4.0\%$) - emergency, 35 ($26.9 \pm 26\%$). 3.6%) and delayed in 36 ($27.7 \pm 3.9\%$). Out of 130 patients, 21 ($16.2 \pm 3.2\%$) were radical, 105 ($80.8 \pm 3.5\%$) had conventional radicals, and palliative interventions in 4 ($3.1 \pm 1.5\%$). executed. In the postoperative period, $15.4 \pm 3.2\%$ (20 patients) experienced various complications. In 610 prospective analyzes, total lethality was $4.8 \pm 0.9\%$ (29 patients): in 480 patients receiving conservative therapy - $4.6 \pm 0.9\%$ (22 patients) and 5.4 ± 130 in 130 patients who underwent surgery. 2.0% (7 people).

Comparative evaluation of STE with betaleukine and AT with 5% mexidol results during conservative and surgical treatment of SCW was performed in 350 patients. Of the 123 patients who received standard complex conservative treatment in the Ia subgroup of the comparison group, 11 ($8.9 \pm 2.6\%$) deaths and 25 ($20.3 \pm 3.6\%$) complications were reported. In the II subgroup of the main group, complications were due to the inclusion of betalexin and 5% mecidol in a set of traditional baseline therapy measures in 11 patients ($10.3 \pm 2.9\%$) and death in 1 patient ($0.9 \pm 0.9\%$).

We have developed a consensus-based clinical practice algorithm of individual differential active treatment tactics, allowing patients to choose specific treatment tactics for each patient in the prospective group, taking into account endoscopic criteria for hemorrhage intensity and prognosis of the probability of RC. .4). Because of the direct relationship between the severity of bleeding, frequency of operations, and the percentage of mortality, the algorithm of choice of the volume of the operation developed by our patients based on the SAPS and ASA scale significantly improved the results of the procedure (Figure 5). The use of a fuzzy module that accurately predicts the relapse of bleeding developed by us, as well as the appropriate treatment tactics and algorithms that allow us to select the volume of surgery, has greatly improved the results of SST and AT. Thus, in 57 of the 57 patients who received traditional baseline therapy after surgical intervention in the Ib subgroup, 13 ($22.8 \pm$

5.6%) had different complications and 4 ($7.0 \pm 3.4\%$) deaths in the II subgroup. In 63 patients undergoing surgical intervention and SST with betaleukine and AT with 5% mexidol in the background of complex baseline therapy, 6 ($9.5 \pm 3.7\%$) had complications and 2 patients died ($3.2 \pm 2; 2\%$). Overall, 103 out of 1501 patients admitted to the clinic with the diagnosis of SCD died (103) ($6.9 \pm 0.7\%$): 74 out of 891 patients ($8.3 \pm 0.9\%$) retrospectively analyzed and 29 in 610 prospective analyzes. ($4.8 \pm 0.9\%$). Of the 746 patients receiving retrospective analysis, conservative therapy was lethal in 56 ($7.5 \pm 1.0\%$) and 22 ($4.6 \pm 1.0\%$) of the 480 patients receiving prospective analysis. Of the 145 patients who underwent retrospectively analyzed and 145 surgical interventions, 18 ($12.4 \pm 2.7\%$) deaths and 41 ($28.3 \pm 3.7\%$) postoperative complications were reported. Of the 130 patients prospectively analyzed and undergoing surgical intervention, 7 ($5.4 \pm 2.0\%$) had fatalities and 20 ($15.4 \pm 3.2\%$) complications. Thus, individual differential active tactics in prospectively analyzed patients could significantly reduce mortality and postoperative complications. Adding betaleukine and mexidol to conventional conservative therapy has decreased the mortality rate in these patients from $8.9 \pm 2.8\%$ to $0.9 \pm 0.9\%$ and the number of complications ranging from $20.3 \pm 3.6\%$ to $10.3\% \pm 2.9\%$. Following standard surgical interventions, the transfer of SST with betaleukine and AT with 5% mexidol and CC progenitor cells transplantation decreased the rate of mortality from $7.0 \pm 3.4\%$ to $4.1 \pm 2.3\%$, and the incidence of postoperative complications from $22,8 \pm 5.6\%$ to $9.6 \pm 3.5\%$.

Thus, in the case of AGDUB, the application of an individual differentiated treatment tactics algorithm, predicting the risk of bleeding recurrence by using a fuzzy module, an algorithm to adequately select the volume of surgery during surgical interventions, inclusion of betaleukin and antioxidant therapy with mexidol in the complex of therapeutic measures, and transfusion of regenerative cord blood cells as during surgical and conservative treatment, it allows to optimize the treatment tactics, which implies These include conducting preventive operations ahead of the recurrence of bleeding, adequate correction of immune deficiency, disorders in antioxi-

dant status and cytokine balance, as well as improving, to a large extent, the results of both surgical and conservative treatment.

FINDINGS

1. In case of gastroduodenal bleeding of ulcer etiology, immunosuppression at the systemic level is characterized in the cellular component of immunity as compared to the norm by a decrease in CD3 + content by 32.9% ($p < 0.001$), CD4 + potential by 32.5% ($p < 0.001$), CD8 + - by 13.3% ($p < 0.05$), the ratio of CD4 + / CD8 + - by 23.2% ($p < 0.001$), phagocytic activity of neutrophils - by 18.9% ($p < 0.001$), in the humoral link against an increase in the level of CD19 + lymphocytes by 58.8% ($p < 0.001$) and CEC by 2.3 times ($p < 0.001$) by disimmunoglobulinemia, a local decrease in lysozyme activity in the gastric juice by 38.3% ($p < 0.001$), in the duodenal contents contentsentratsii IgA, M and G to 72,0% ($p < 0,001$), 55,1% ($p < 0,001$) and 37,6% ($p < 0,001$), respectively [22].

2. With gastroduodenal ulcer bleeding at the systemic and local level, a cytokine imbalance is observed, which manifests itself in an increase in the concentration of proinflammatory cytokines TNF α - 5.7 times ($p < 0.001$), IFN γ - 5.4 times ($p < 0.001$), IL-1 - 9.9 times ($p < 0.001$), IL-2 - 8.7 times ($p < 0.001$), IL-6 - 12.8 times ($p < 0.001$), IL-8 - 2.5 times ($p < 0.001$), the concentration of anti-inflammatory cytokine in IL-4 - 6.2 times ($p < 0.001$), and vice versa, a decrease in the content of IL-10 by 45.2% ($p < 0.001$), as well as an increase in the concentration of IL- 6 in urine - 8.2 times ($p < 0.001$) and a decrease in gastric juice - by 37.5% ($p < 0.001$) [22].

3. When gastroduodenal bleeding of ulcerative etiology in the antioxidant status of the body at the system level, an imbalance develops in the form of an increase compared with the normal concentration in the plasma of DC - 2.8 times ($p < 0.001$), MDA - 2 times ($p < 0.001$), catalase by 17.8%, in red blood cells of GP and OAA by 8.4% and 17.1%, respectively, on the contrary, a decrease in the level of QSH - by 25.0% ($p < 0.001$), an increase at the local level of DC and MDA in biopsy samples taken from the edge of a bleeding gastric ulcer 2.2 ($p < 0.001$) and 3.1 times ($p < 0.001$), respectively, and

in biopsy samples of a duodenal ulcer, an increase in the content of DC by 89.3% ($p < 0.001$) and MDA 2.9 times ($p < 0.001$) [22].

4. With gastroduodenal ulcer bleeding at the local and systemic levels, the depth of immunosuppression of the imbalance in the cytokine and antioxidant status directly depends on the severity of blood loss: with an increase in the volume of lost blood, immunosuppression and an imbalance of cytokines and antioxidants are aggravated. In these patients, there is a direct correlative relationship between the systemic and local indicators of the immune, cytokine, and antioxidant statuses, which depends on the depth of the blood loss volume [43].

5. In the conservative and surgical treatment of gastroduodenal bleeding of ulcer etiology, the inclusion in complex therapy of individual doses of recombinant IL-1 β - betaleukin and antioxidant mexidol, having a more effective effect on immunosuppression, increases the content of CD3 + lymphocytes by 31.7% ($p_0 < 0.001$), CD4 + - by 31.6% ($p_0 < 0.001$), the ratio of CD4 + / CD8 + - by 22.6% ($p_0 < 0.001$), FI - by 15.4% ($p_0 < 0.001$), reduces the level of CD19 + cells - by 23, 6% ($p_0 < 0.001$), CEC - by 37.9% ($p_0 < 0.001$), eliminating disimmunoglobulinemia and sharply reducing the intensity of lipoperoxidation accelerates normalization of endogenous intoxication and antioxidant defense [32, 35].

6. Against the background of complex treatment of gastroduodenal bleeding of ulcerative etiology, individually differentiated targeted immunostimulation - cytokine therapy with betaleikin, on the 14th day of observation reduces the increased concentration of TNF α by 43.7% ($p_1 < 0.001$), IFN γ by 41.4% ($p_1 < 0.001$), IL-1 - by 52.7% ($p_1 < 0.001$), IL-2 - by 65.9% ($p_1 < 0.001$), IL-6 - by 48.7% ($p_1 < 0.001$), IL- 8 - by 29.5% ($p_1 < 0.001$), IL-4 - by 60.7% ($p_1 < 0.001$), on the contrary, increases the level of IL-10 - by 17.9% ($p_1 < 0.05$) and accelerates the elimination cytokine imbalance [30, 31].

7. In the most severe contingent of patients in the postoperative period, within the framework of generally accepted basic therapy, transplantation of cryopreserved cord cells is a pathogenetically substantiated more effective immunostimulating method, which makes it possible to eliminate immunosuppression and cytokine imbalance in

a short time, improves the clinical course of the disease and normalizes the level of hemoglobin and red blood cells [15].

8. The clinical application of the method we developed that predicts the risk of recurrence of bleeding with a fuzzy module, based on the theory of fuzzy logic, taking into account clinical endoscopic immunological criteria, allows you to choose the optimal treatment tactics, objectively justify the indications for surgical interventions that can get ahead of a recurrence of bleeding [33].

9. The treatment tactics algorithm developed by us, taking into account endoscopic criteria for the intensity and risk of bleeding recurrence, allows you to correctly select the conservative or surgical method for each patient, as well as determine the indications for operations and the timing of their conduct, thereby having a positive effect on the treatment results [35, 36].

10. For gastroduodenal ulcer bleeding, an integrated approach based on the fuzzy module method - the most reliable prediction of the risk of recurrence of bleeding - an algorithm that makes it possible for each patient to choose a treatment method and correctly determine the indications for surgery, by assessing the severity of patients on the SAPS scale and anesthetic risk according to ASA contributes to the correct choice of the volume of surgery, and the inclusion in the complex of basic therapeutic measures - directed differentiated immunocorrection of cation and antioxidant therapy can reduce the overall mortality from 8.3% to 4.8% (OS = 0.55%; 95% CI 0.35 - 0.76; $p < 0.05$), mortality with conservative treatment from 7, 5% to 4.6% (OS = 0.59; 95% CI 0.36 - 0.98; $p < 0.05$), postoperative mortality from 12.4% to 5.4% (OS = 0, 40; 95% CI 0.16 - 1.00; $p < 0.05$) and the incidence of various postoperative complications from 28.3% to 15.4% (OR = 0.46; 95% CI 0.25 - 0, 84; $p < 0.05$) [36].

PRACTICAL RECOMMENDATIONS

1. It is advisable in the hospital for early prediction of the likelihood of recurrence of bleeding to use our proposed method of fuzzy module.

2. In case of gastroduodenal ulcer bleeding, it is recommended to use the treatment tactics algorithm developed by us that is specifically designed for each patient to select therapeutic tactics, determine indications for surgery, and select the volume and urgency of surgical intervention.

3. To eliminate immunosuppression, cytokine and antioxidant imbalances, as well as to improve treatment outcomes, both with conservative and surgical treatment with stable hemostasis, it is advisable to include in the complex of measures of basic therapy in the following regimen betaleukin and 5% mexidol in physiological solution for 2-3 hours:

1. With a mild degree of blood loss:

- betaleukin in a dose of 0.5 mcg once a day, only 3 days
- Mexidol 2.0 ml once a day, only 3 days

2. With moderate blood loss:

- betaleukin at a dose of 1.0 mcg once a day, only 3 days
- Mexidol 2.0 ml twice a day, only 3 days

3. In severe cases of blood loss:

- betaleukin at a dose of 1.0 mcg once a day, only 5 days
- Mexidol 2.0 ml twice a day, only 7 days.

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List of abbreviations

- ACC - aminocaproic acid
AOD - Antioxidant Defence
GP - glutathione peroxidase
DC - diene conjugates
PPI - proton pump inhibitor
CAT - Catalase
CB - cord blood
MDA - malondialdehyde
TAA - total antioxidant activity
AGDUB - acute gastroduodenal ulcer bleeding
LPO - lipid peroxidation
RB - relapse of bleeding
SC - stem cells
MMP - medium molecular peptides
BRPS - bleeding relapse prediction system
SCT - systemic cytokine therapy
PHI - phagocytic index
PhA - phagocytic activity
FEGDS - fibroesophagogastroduodenoscopy
CIC - circulating immune complex
GSH - reduced glutathione
Hp - Helicobacter pylori
IFN γ - interferon gamma
IgA - immunoglobulin A
IgG - immunoglobulin G
IgM - immunoglobulin M
IL - interleukin
TNF - tumor necrosis factor

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