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PAPER FOR OBTANING OF THE DOCTOR'S DEGREE

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HARALDS PLAUDIS

EARLY ORAL FEEDING IN PATIENTS WITH SEVERE ACUTE PANCREATITIS

SUMMARY OF DIPLOMA PAPER FOR OBTANING OF THE DOCTOR'S DEGREE

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ABBREVIATIONS

AP – acute pancreatitis

SAP – Severe acute pancreatitis

SIRS – Systemic inflammatory response syndrome

MODS – Multiple organ dysfunction syndrome

Probiotics – mostly lactobacteria and bifidobacteria that can colonise human gastrointestinal tract

Prebiotics – soluble fibres (oligosaccharides)

Synbiotics – mixture of prebiotics and probiotics

CVVH – continuous veno-venous haemofiltration

APACHE II – Acute Physiology and Chronic Health Evaluation scoring

SOFA – Sequential Organ Failure Assessment

CRP – C-reactive protein (marker of inflammation)

IAP – intraabdominal pressure

IAH – intraabdominal hypertension

ACS – intraabdominal compartment syndrome

SD – Standard deviation

EN – enteral nutrition

ICU – intensive care unit

ARDS – acute respiratory distress syndrome

MALT – mucosa associated lymphoid tissue

GALT – gut associated lymphoid tissue

1. INTRODUCTION

1.1. ACTUALITY OF THE STUDY

Severe acute pancreatitis is still a very urgent problem in the emergency medical care; this problem is tackled by surgeons, the ICU specialists and gastroenterologists, as well as by the representatives of other specialties. An important prerequisite for successful final outcome of the treatment is timely diagnostics of severe forms of the disease, which provides the possibility to considerably decrease the risk of the development of complication and the frequency of infected necrosis; consequently it reduces the length of ICU treatment and the overall hospitalization time. The aforementioned factors have notable influence on the total costs of treatment and the quality of patient's life after the treatment.

The application of progressive methods of diagnostics and precise compliance with the protocol in ICU for such patients within the framework of medical care has considerably decreased the number of complications and lethality; however the results are still not satisfactory. The total rate of lethality in the group of severe acute pancreatitis (SAP) ranges from 30 to 50%, and in cases of infected necrosis it even reaches 70%. An essential factor is timely diagnostics and therapy of infected necrosis, though the most important is to prevent the infection of necrosis. Many multi-center clinical studies (Isenmann et al, Dellinger et al and etc.) have proven the importance of antibacterial therapy in both the prophylactics of infection and the treatment of infected necrosis, however the statistic data do not prove that there is a considerable decrease in the risk of infection and total lethality for the group of patients that have been treated with antibiotics. The aforementioned fact underlines that there is an essential necessity for new, effective methods and their application in order to reduce the total risk of the infection and consequently - the lethality.

The world publications of the recent years more and more bring forward the issue on the importance of the alimentary system in pathogenesis of systemic inflammatory response syndrome (SIRS). 70-80% of immune-competent cells of the body are located in the

alimentary tract, which proves that the alimentary system has the leading role in the coordination of systemic inflammatory response. Many authors believe that the alimentary system is the brain that drives immune response; it emphasizes its role in ensuring the physiological response of the organism. The alimentary system contains millions of various type bacteria; they play an important role in both splitting the nutrients and in the maintaining of the gut barrier function, which consequently is extremely important in the modeling of the inflammatory response. Many studies have proven the role of dysbacteriosis in cases of ulcerative colitis, Crohn's disease, rheumatoid arthritis and other systemic autoimmune diseases. The fostering of the barrier function of the alimentary tract plays important role within the framework of the above mentioned disease therapy plans.

Currently one of the most topical themes in the world publications is the inflammatory response (acute inflammation and chronic inflammation) and the response of the organism on it. No one acute or chronic pathology passes without the inflammatory response. The inflammatory response appears as the response on an aseptic cause (for example, rheumatoid polyarthritis, acute pancreatitis) or a septic cause (for example, abscess). The physiological responses are identical in both cases. It brings forward the question on modulation possibilities of the aforementioned physiological responses in the organism, so that the inflammatory response was not too “weak” or too overwhelming.

Currently one of the most topical fields of research is providing the alimentary tract of a patient with various immune model substances with the aim to strengthen the gut barrier function. This principle is called immunonutrition. Initially the standard enteral nutrition formulas were supplemented by various amino-acids and polyunsaturated fatty acids. Nowadays there has been more advanced research and the alimentary system is supplemented by fibrous matter (prebiotics), bacteria (probiotics) or the mixture of the both substances (synbiotics). There are scientific data that prove the ability of prebiotics, probiotics and synbiotics to modulate systemic inflammatory response in a positive way and in the result of strengthening the intestinal barrier function it decreases the number of complications. Currently there are a number of clinical studies carried out in the world on

the efficiency of synbiotics in cases of pulmonary and systemic disease, as well as in the treatment of surgical sepsis. Though, until now there have not been any publications about the data obtained by double blind multi-center studies that prove the efficiency of synbiotics therapy.

The theme of PhD thesis fits into the field of current most topical international research. The topicality of the study is defined especially by double blind randomized research protocol in the research on clinical efficiency of synbiotics therapy in the group of patients with severe acute pancreatitis; until now it has not been done neither in Latvia nor outside its borders. Thus it can be forecasted that the results of the research will be internationally recognized and meaningful for the research made into this field.

1.2. NOVELTY OF THE STUDY

1. The enteral nutrition forms for the patients with acute surgical pathology will be supplemented with prebiotics and synbiotics for the first time in Latvia.
2. The supplements of synbiotics and prebiotics in patients with acute surgical pathology for the first time in Latvia and in the world will be supplied in peroral way instead of using probe feeding.
3. Double blind randomized research on the importance of synbiotics/prebiotics in the SAP therapy schedule will be made for the first time in Latvia.
4. The supplements of synbiotics and prebiotics for the first time in Latvia and in the world will be added to small volume small calorie enteral nutrition protocol.
5. The supplements of nutritive mixtures will be supplied at the initial stages of the disease, which permits to assess the efficiency of the therapy very early in the course of the disease.

1.3. PURPOSE OF THE STUDY

To compare the efficacy of standard enteral feeding formula, standard enteral feeding formula + fibres and standard enteral feeding formula + Synbiotic 2000 FORTE in the

modulation of inflammatory response, enhancement of the organ function, improvement of the gut barrier function and improvement of the transit.

1.4. STUDY OBJECTIVES

1. To enroll in each study group about 30 SAP patients to ensure statistical strength of obtained results;
2. To ensure early enteral nutrition for the purpose of intestinal transit and intestinal barrier renewal by using standard enteral nutrition formulas, standard enteral nutrition formulas + fibers or standard enteral nutrition formulas + Synbiotic 2000 FORTE depending on the results of randomization;
3. To ensure full conservative therapy complex for SAP patients at ICU, and in surgical department;
4. To perform statistic processing and analysis of the obtained data, in order to establish the efficiency of synbiotics and prebiotics use for the patients with severe acute pancreatitis.

1.5. PRACTICAL APPLICATION OF THE STUDY

The study has proved that early peroral supplementation of nutrition scheme with synbiotics/prebiotics for SAP patients is possible and that the results of mixture tolerance are good. Early small volume and small caloricity peroral nutrition is effective and substantially decreases the development of septic complications. The synbiotic/prebiotic supplements considerably improve the gut barrier function; thus they reduce the level of infected necrosis. Due to the application of the aforementioned formulas there is a notable decrease in the length of ICU and in the total hospital stay and lethality in comparison with the cases when standard enteral nutrition formulas were used. The enteral nutrition in small volumes is recommended and possible for the patients with the dysfunction of alimentary tract, as well as for the patients with intra-abdominal hypertension and it has considerable influence on the intestinal function

renewal. Synbiotic/prebiotic supplements are recommended for the patients with SAP, and there should be considered their application in cases of other acute pathologies (peritonitis, pneumonia, sepsis and etc.).

2. REVIEW OF THE LITERATURE

2.1. SAP DEFINITION

Acute pancreatitis is a pathological condition in the pancreas; it is based on the loss of integrity of acinar cells of the gland in the result of microcirculation disturbances; it involves the damage of cell membranes and activation of intracellular lyzosomal and proteolytic enzymes. In mild cases there appears the apoptosis of cells and limited cell necrosis; it causes the inflammatory response of local surrounding tissues. In more severe cases the necrobiotic process affects larger part of the gland and peripancreatic area, consequently there develops a severe local and systemic inflammatory response; and if it grows more serious it can cause multiorgan dysfunction syndrome and death.

2.2. EPIDEMIOLOGY OF SAP

Until now the treatment of patients suffering from severe acute pancreatitis (SAP) is a serious challenge for surgeons and intensive care specialists. Increasing number of SAP patients is observed worldwide and characterizes last year tendency.

The main risk groups are the same including those who abuse alcohol and patients with gallstone disease, which has not been cured in a timely manner. However, during the last years new risk groups have emerged including patients with severe dyslipidemia and/or metabolic syndrome. Despite the rapid implementation of the modern technologies and new treatment modalities in the modern intensive care, numbers of fatal outcomes in the group of patients suffering from SAP still remain high. Taking into consideration statistical data showing that considerable number of SAP patients are young and economically active people, evident is importance of early diagnose and effective

treatment in order to diminish the costs of the therapy and to improve the quality of life of patients in a later stage.

Since 1999 “Acute and chronic pancreatitis” research team has been working in the Clinical University Hospital “Gailezers”. Diagnostic and therapy algorithm of SAP has been developed and implemented during these years. Data collection and recording have been performed on average for 60 SAP patients annually. Main results have been presented at the international meetings and published in internationally recognized magazines. Everyday clinical practise and problem orientated research resulted in to the priceless experience and advancement of the therapeutic strategy towards higher clinical standards.

2.3. PATHOPHYSIOLOGY

Primarily the tissue damage involves only acinar cells of the pancreas, however already after some seconds rapid proinflammatory cytokine secretion takes place, which in several minutes, results in amended activity of coagulation and fibrinolysis, then at last after several hours definable changes in active stage proteins takes place. Inflammation rapidly spreads to the gastrointestinal tract, in which approximately 80% of the cells forming immune system are located, especially to the large intestine. Cytokines secreted by the immuno-competent cells, products of tissue destruction and mediators cause certain local and systemic response reactions, the intensity of which has a significant role in the further development of the disease.

2.4. STAGES OF INFLAMMATION

It is well known that the clinical course of the disease is characterised by two phase: early stage (the first two weeks of disease), when systemic inflammatory response syndrome (SIRS) as well as multi organ dysfunction syndrome (MODS) is dominant and late stage (starting with the third week of the disease) when the clinical course of the disease is

determined by peripancreatic infection and sepsis, mainly in cases of necrotic forms. Already from the start severe inflammatory response influences lung function it is followed by impaired renal function and coagulation disturbances. Infection with progressing sepsis and development of the late MODS in cases of necrotizing forms is the main reason for the increased lethality in the second stage of the disease. In cases of infected necrosis lethality reaches even 70%. Adequate and timely intensive care, based on organ support and prophylaxis of sepsis, has significant impact on development of early and late complications. Application of the intensive care principles and early enteral feeding makes possible modulation of the immune response decreasing septic and systemic complications.

2.5. ROLE OF GUT BARRIER (MICROFLORA)

Functions like digestion of nutrients, binding of digested nutrients to transport proteins and transfer them into the blood stream, detoxication function of gastrointestinal tract is widely known. Gastrointestinal tract is a home for specific microflora, which also has a significant role in the digestion processes and ensuring of humoral immunity. Microflora is unique in every particular person and it changes during the life, this process is influenced by different factors of environment, food consumption traditions and diseases. The following functions of gastrointestinal tract microflora are known:

1. formation of nutrients for mucous membrane: acetates, butirates, propionates, piruvates, amino acids (arginine, cysteine, glutamine);
2. formation and excretion of various micronutrients: histamine, piperidin, tyramine, cadaverine, putrescine and others;
3. regulation of potential pathogen microorganism concentration by prevention of their overproduction;
4. stimulation of intestinal immunity especially the GALT (gut associated lymphoid tissue) system via the production of endogenous NO;
5. elimination of toxins from the gastrointestinal tract;

6. impact on the motility of gastrointestinal tract, regulation of bowel perfusion, digestion of mucus etc.

Protective function of gastrointestinal tract is subjected to the influence of different factors – stress, western diet in which there are very small amounts of fibres and polyunsaturated fatty acids. These factors can lead to serious dysbiosis that is the reason for the development of different gastrointestinal complaints and can seriously influence barrier function of the gastrointestinal tract. Such situations have been described in astronauts who have been on low fibre diet for a long time. However, in present days, the numbers of such "astronauts" living among us are increasing.

Immune function and especially gut barrier are the most significant functions of the gastrointestinal tract considering systemic inflammatory response. Immuno-competent cells, which have been collected in two large and significant systems MALT (mucosa associated lymphoid tissue, immuncompetents cells that are located in mucosa) and GALT (gut associated lymphoid tissue, Peyer's patches, mesenteric lymph nodes etc.) are ensuring the immune function of the gastrointestinal tract. Small intestines receive approximately 50% from the necessary nutrients intraluminally, on the contrary the large intestine >80% of nutrients receive from the lumen. Gastrointestinal tract is not able to receive feeding from the blood stream only. Bacteria perform this important feeding function. Significant mucous membrane atrophy takes place during the first hours in patients who receive parenteral feeding only. Consequences of intestinal fasting are atrophy of lymphoid follicles, defective regeneration of mucous membrane, defective IgA synthesis finally resulting in the proliferation of the pathogenous microflora. In addition, the gastrointestinal barrier function is negatively influenced by different medications like nonsteroidal anti-inflammatory drugs and critical tissue hypoperfusion. As a result atrophy of the mucous membrane with following weakening of the gastrointestinal barrier appears. The risks of nosocomial infection increase rapidly for these patients.

Assessment of the intestinal barrier function is a significant aspect, which indirectly allows to evaluate condition of the patient's immune system, and make prognosis on the clinical development of the disease and efficacy of the applied treatment. Assessment of

the infectious complication rate indirectly and inspecting biopsy specimens of the mucous membrane from the rectum wall can directly evaluate gut barrier function. A specific test such as Lactulose/Mannitol test has limited value in the critical care setting.

2.6. APPLICATION OF ENTERAL NUTRITION

Historically large number of authors rejected application of enteral feeding in patients suffering severe acute pancreatitis by grounding this opinion with thesis about the stimulating effect on pancreas secretion by this treatment modality. The opinion, that secretion of pancreatic enzymes can increase the process of autodigestion of the gland and activate the inflammatory response, has been propagated. Currently wide discussions about early application of parenteral feeding or early application of enteral feeding are not present. Numerous clinical studies have proven the advantages of the enteral feeding in comparison with parenteral feeding. Enteral feeding is the most physiological and effective way how to deliver nutrients for the intensive care patients. Early enteral feeding is cheaper, more physiological and easier to accomplish than parenteral feeding, it improves perfusion of intestines, normalise flora, and improves healing processes of anastomosis. Early enteral feeding is the most rational way of nutrient delivery in SAP patients and in patients after vast surgeries of gastrointestinal tract. Dysfunction of gastrointestinal tract as a consequence of MODS has been mentioned as a serious contra argument for early application of the enteral feeding with possible increased risk of enteral feeding related complications. Whereas other authors consider that enteral feeding improves barrier function of gastrointestinal tract and diminishes the possibilities of the post operative bowel obstruction. However, the main advantage of the enteral feeding is stabilization of the gastrointestinal tract integrity and thus modulation of the acute inflammatory response.

The way in which the specific feeding formulas have been transferred into gastrointestinal tract is of significant importance. It is postulated that the least stimulating effect on the exocrine function of the pancreas is transfer of nutrients into the proximal

part of the small intestines with the help of a probe. However, leading SAP treatment group from the United Kingdom has published data about the intra-gastric feeding experience in this category of patients with very low complication rate, considering this type of feeding to be feasible and safe. On the grounds of this study in year 2001 we started clinical study on early oral enteral feeding formula supplementation without using a probe. Patients who were able to sip water started to take enteral feeding formula orally. Preliminary results were promising and at present administration of the enteral feeding formulas orally is a clinical routine.

Administration of dosed specific feeding blends into gastrointestinal tract is the most effective way to modulate immune response and to increase the capacity of bodily resistance. Recent meta analysis of six randomized clinical studies has proven that enteral feeding in comparison with parenteral feeding decreases number of septic complications, necessity for surgical interventions and duration of hospitalization, however it does not decrease lethality and possibility of the development of non infectious complications.

Taking into consideration international publications of the last years the question on enteral feeding formula administration roots, blend schemes and their contents, administration speed and also calorie supply has been actualized more often. Current guidelines consider that enteral feeding would have to ensure 25 kcal/kg/daily; this principle is called "goal feeding". Clinical practice proves that nutrient delivery according to formerly recommended volumes especially in patients with SAP is practically impossible to provide without associated gastrointestinal and metabolic complications. Numerous authors and international publications strictly object the principle of "goal feeding". They consider that overfeeding may cause more serious consequences than small volume enteral feeding.

Important issue is addition of the specific immunmodulating components into the enteral feeding schemes. This principle is called immunonutrition. Various amino acids (arginine, glutamine etc), ϖ-3 polyunsaturated fatty acids, fibres and probiotic bacteria are considered to be such specific components. Addition of specific compounds to the scheme of enteral feeding improves motility of gastrointestinal tract, strengthen gut

barrier function and early modulate bodily immune functions and thus immune response, which is especially important in the prognosis of the disease.

2.6.1. Synbiotics

Taking into consideration current SAP treatment guidelines, the rational of application of synbiotics in the scheme of the enteral nutrition has become widely discussed. Experimental studies, which have been performed on animals, have proven that early addition of synbiotics into the feeding scheme diminishes the activity of neutrophil leukocytes and tissue oxidative stress. Inclusion of synbiotics into the enteral feeding schemes of patients with SAP allows more effectively modulate gut barrier function and decrease number of early and late septic complications. Recent experience from the international publications indicates that synbiotics possibly has capacity to modulate systemic inflammatory response syndrome. Therefore it can be considered that application of synbiotics can positively influence clinical course of the disease and diminish development of complication.

2.6.2. Prebiotics

Currently several types of fibres are established. All fibres are divided in three groups according to their ability to dissolve in water. Deliquescent fibres have quality to improve intestinal metabolism and glucose tolerance, they attach bile acids, diminish circulating fatty acids and cholesterol level and finally they are integral nutrients for the intestinal flora. Optimal microclimate for the digestion is maintained by splitting fibres in the gastrointestinal tract. Fibres help form the protective layer of epithelium in which lactobacteria proliferate and live. Layer of mucus is significant in the metabolism and protects epithelial cells from different toxic factor influence and ensures barrier function. Fibres work also as serious antioxidants thus stimulating GALT system and improve bodily immunofunction.

2.6.3. Probiotics

Lactobacteria are very important part of our gastrointestinal tracts. Their functions are not only to help to split various nutrients but also to promote bodily immunofunction and to ensure the barrier function of gastrointestinal tract. Depending on the ability with specific receptors to bind to the layer of epithelium probiotic bacteria have been divided in adhesive and nonadhesive. The largest part of bacteria, that can be found in commercially available yoghurts, cheeses, and other fermented milk products, does not have ability to bind to the epithelial cells and therefore colonize gastrointestinal tract (*Enterococcus thermophilus, L. bulgaricus, L. acidophilus*, major part of *Bifidobacteria* stem.etc.). While definite product is being consumed the patients is benefiting from the qualities of probiotic bacteria, effect rapidly diminishes after the end of consumption. Approximately only 500 probiotic bacteria stems have shown the ability to bind to the epithelial cells and to colonize gastrointestinal tract. Such stems would be: *L. acidophilus* LA, *Lactobacillus plantarum* 2362, 299, *Pediacoccus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei* subsp *paracasei* 19 and others. Lactobacteria have the ability to prevent binding of relatively pathogenous bacteria to epithelial cells, they are most important in strengthening of gut barrier function.

3. INCLUSION CRITERIA

1. Patients 18-80 years old;
2. Patients suffering severe acute pancreatitis with the following parameters:
    a. CRP (C-reactive protein) in blood serum ≥ 200 mg/L;
    b. Lipase activity three times above normal plasma levels (>180 U/L);
    c. SIRS and/or signs of organ dysfunction.
3. By ultrasound scan and/or computer tomography proven intra-abdominal or retroperitoneal fluid collections in more than two localizations;
4. Conscious patients with no serious intestinal transit disturbances that can sip water (intra-abdominal pressure < 15 mmHg).

4. EXCLUSION CRITERIA

1. Patients not meeting any of the inclusion criteria;
2. Patients with suspicions of oncological process or advanced oncological diseases;
3. Patients with pronounced signs of immunosupression;
4. Haemodinamically unstable patients who would need pressure support for more than 5 days;
5. Patients who cannot drink liquids;
6. Patients with significant intestinal transit disturbances who would not be able to start enteral nutrition protocol in 5 days since the moment of hospitalization.

5. TREATMENT PROTOCOL

5.1. IN THE ADMISSION ROOM THE FOLLOWING SHOULD BE ASSESSED:

1. Clinical condition according to the inclusion/exclusion criteria;
2. Systemic inflammatory response syndrome;
3. Signs of organ dysfunction;
4. Visual diagnostics: USG, chest and abdominal X-ray;
5. Clinical laboratory tests (blood analysis, clinical biochemistry, including lipase and CRP);
6. Endoscopic, CT and other visual diagnostics upon necessity;
7. ECG for the patients older than 50.

5.2. IN THE INTENSIVE CARE UNIT

The disease severity assessment:

- by counting APACHE II score (during admission);
- signs of SIRS;

- evaluation of SOFA score (see Appendix 2);
- IAP measurements;

1. Defining of treatment tactics for the nearest 24 hours in coordination with the surgeon involved;
2. Preparation for the first necessary surgery and choice of the extent of surgery in cooperation with anaesthesiologist, surgeon and specialist from ICU;
3. Evaluation of the patient status in dynamics:
   - Monitoring of vital signs – 24 h/day;
   - Standard biochemical tests – 1x/day or upon the necessity;
   - Control of intra-abdominal pressure (IAP) – 2x/day;
   - Sampling of acute phase proteins: CRP, fibrinogen – on admission, on the third day counting from the start of disease and every 3rd day until the stable regression of SIRS;
   - Blood gas analysis – on admission, depending on the prescription of specialists from ICU or every third day until the stable regression of SIRS;
   - Bacteriological examinations mandatory for the patients with severe acute pancreatitis should be done during the operation and blood culture before operation (in cases of suspected septicaemia). The frequency of sample recollection is determined by the specialists working on the protocol;
4. Main principles of conservative treatment of SAP:
   - Ensuring of organ perfusion, including colloids (isovolemic haemodilution);
   - Organ support therapy;
   - Renal replacement therapy;
   - Early enteral feeding by application of the standard enteral feeding formulas, blends of standard enteral feeding formulas + fibres or blends of standard enteral feeding formulas + Synbiotic 2000 FORTE according to the scheme with test dose (20ml every 2 hours) in compliance with the results of randomization;

- Parenteral feeding would be applied in patients with SAP only in cases when the enteral feeding has failed during the period of 5 – 7 days by strict control of glycaemia.

5. Evaluation of clinical course of disease and treatment efficacy:
   - On admission the severity of disease is evaluated in accordance with APACHE II scale;
   - Clinical course of disease is monitored upon dynamics of organ dysfunction by evaluating SOFA scale every day;
   - Visual diagnostics upon indications: US and X-ray examination on admission, CT, MR and other methods upon additional indications.

5.3 TREATMENT IN THE SURGICAL DEPARTMENT

Treatment at the surgical department should be provided in accordance with the specialist that is involved in the protocol. Doctor who is in charge for the patient is responsible for obtaining of all clinically important laboratory data, prescribing CT scans and providing conservative treatment protocol in accordance to the protocol.

6. MATERIALS AND METHODS

90 patients with severe acute pancreatitis have been enrolled into a randomized, double blind, prospective study since July 2005. Severe acute pancreatitis has been classified according to Atlanta 1992 criteria.

APACHE II criteria on admission, signs of SIRS and MODS, serum C-reactive protein, lipase activity, changes in intra-abdominal pressure and number of infectious complications have been monitored and evaluated in dynamics. Number of complications, ICU days and overall hospital stay, mortality and tolerance of enteral feeding has been evaluated and compared among the groups.

Totally 76 patients have been treated in the ICU during their hospital stay. Initial intensive monitoring and treatment have been provided in the step down ICU of the surgical department with transfer to the regular surgical ward for 14 patients. Diagnosis of severe acute pancreatitis has been based on typical clinical picture, increased of plasma lipase activity 3 times UNL and on one of the additional criteria: severe SIRS and/or early MODS (first 48 hours after hospitalization), APACHE II score on admission ≥ 6. Diagnosis of necrotic pancreatitis has been stated when during ultrasound examination or computer tomography with contrast media peripancreatic or pancreatic necrosis has been confirmed. For all patients who have been subjected to computer tomography with contrast media in any stage of the treatment Baltazar score has been calculated. Computer tomography has been performed in cases when patient has been transferred from ICU to surgical department, for diagnostics of infection, in cases of differential diagnosis and late complications as well as for evaluation of tactics for the further therapy. Additional parameter for diagnosis of necrotizing pancreatitis has been presence of necrosis during the surgery and/or plasma CRP ≥ 200 mg/L.

Organ dysfunction was defined according to the recommendations of the Consensus Conference of American College of Chest Physicians/Society of Critical Care medicine in 1991. SIRS has been defined in case at least two of the following parameters were positive, as a consequence of infection or aseptic inflammation:

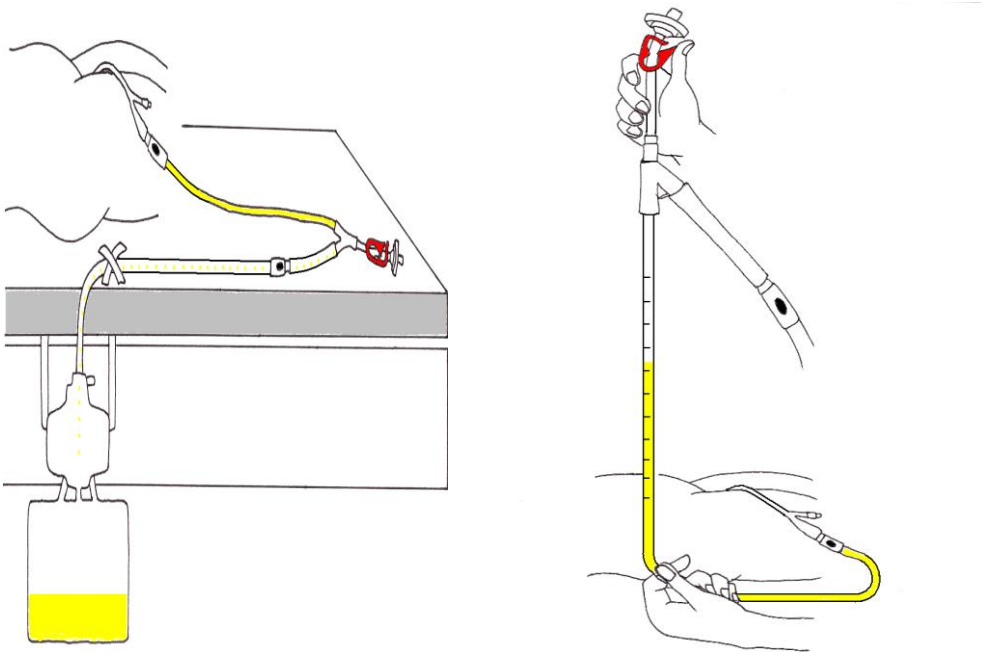
- temperature above 38°C or below 36°C
- tachycardia above 90 x/min
- tachypnoe 20 x/min or $PaCO_2$ below 32 mmHg
- leukocytosis above 12000/mm^3 or below 4000/mm^3, or new forms above 10%.

A MODS has been diagnosed if at least dysfunction of two organs has been found for which organ support therapy was necessary. Dynamics of MODS have been evaluated by calculation of daily SOFA score, the sum of which determined the stage of organ dysfunction.

Diagnosis of radiologically confirmed basal atelectasis, ARDS, pneumonia or pleural exudates have been registered separately from pulmonary dysfunction and defined as pulmonary complications.

Intra-abdominal pressure (IAP) has been measured indirectly via catheter inserted into urinary bladder and enteral feeding has been initiated in cases when IAP was < 15 mmHg.

Picture 1. Technique of IAP measurement.



Increase of IAP > 12 mmHg has been considered as intra-abdominal hypertension, intra-abdominal compartment syndrome has been defined as increase of the IAP > 20 mmHg in association with one new organ dysfunction.

Recurrence of SIRS (late SIRS, most often starting with the third week), worsening of patient's general condition, signs of recurrent organ dysfunction has been considered as indicator of infected necrosis. Computer tomography with contrast medium has been performed as additional diagnostic criteria. Peripancreatic air bubbles or abscesses on CECT proved presence of infection. Fine needle aspiration biopsy was not used on routine basis for confirmation of infection. Blood cultures have been collected when signs

of sepsis were present. Positive results have been registered separately from peripancreatic infection. Two types of peripancreatic infections have been defined:

1. Primary infection – when during surgery infected necrosis has been confirmed and positive bacterial cultures have been received from bacteriological laboratory.
2. Secondary infection (drain related infection) – there have not been signs of infected necrosis during the first surgery, negative bacterial culture. Infection has occurred during the late stage due to continued drainage.

All enrolled patients have received standard enteral feeding in addition to complex scheme of therapy, which has been based on early organ support therapy, normalization of tissue perfusion and restriction of the fluid loses in the third space (tissue oedema). Therapy has been based on adequate fluid replacement according to the principle of the isovolemic haemodilution and early continuous veno-venous haemofiltration (CVVH). Indications for early CVVH have been severe SIRS, early MODS or rapid progression of intra-abdominal compartment syndrome (IAP > 20 mm/Hg) in the first 48 hours from hospitalization despite complex non-invasive therapy. Haemofiltration has been done with B.Braun Co Diapact CRRT renal replacement therapy and Fresenius Medical Care Multifiltrate machines.

The basic antibacterial agents have been fluorochinolones and metronidozole or imipenem/cilastin monotherapy in cases when strict indications have determined the choice. Change of antibacterial therapy has been done in cases of infected necrosis upon receipt of susceptibility results from bacteriological laboratory or upon the clinical situation. Totally 13 patients have not received any antibacterial therapy during their treatment. Enteral feeding has been initiated for conscious patients who consented their participation in study without impaired function of gastrointestinal tract (without nausea and vomiting, with normal bowel sounds and possibility to insert the probe). According to the results of randomization patients have been divided into three groups.

Group I – patients receiving standard enteral feeding formula according to the protocol and complex intensive care protocol according to the standard of severe acute pancreatitis (Control group).

Group II – patients receiving standard enteral feeding formula with Synbiotic 2000 Forte added according to the protocol and complex intensive therapy protocol according to the standard of severe acute pancreatitis treatment.

Group III – patients receiving standard enteral feeding formula with fibres added according to the protocol and complex intensive therapy protocol according to the standard of severe acute pancreatitis treatment.

Enteral feeding protocol – standard enteral feeding formulas or their blends with immunomodulating additives initially have been administered with the speed of 20 ml every 2 hours. Gradually the dose has been increased until 20 ml in hour. In cases when patients tolerated initial feeding well, feeding rate has been increased along until 50 ml per hour under monitoring of individual tolerance. Feeding has been ensured taking into consideration the principle to feed the gut and not to try to administer the necessary average 2500 kcaL a day. Standard enteral feeding formulas used (Group I) contained 1 – 1.5 kcal/ml (Nutrison Standard Nutricomp or Nutridrink, Nutricia). On average after two days besides the enteral feeding patients started to eat oatmeal soup and natural yoghurts, later being transferred to the hospital food. Intrahospital feeding included blended vegetables, minced chicken and/or fatless fish.

Additives to synbiotics (Group II) (Synbiotic 2000 FORTE™) contained prebiotics (blend of four well known bioactive fibres):

- 2.5 g beta-glucane
- 2.5 g inuline
- 2.5 g pectin
- 2.5 g resistant starch, in total 10 g of herbal fibres

and probiotics:

- 10^{11} *Pediacoccus pentosaceus* 5-33:3

- 10^{11} *Leuconostoc mesenteroides* 32-77:1
- 10^{11} *Lactobacillus paracasei* subsp *paracasei* 19
- 10^{11} *Lactobacillus plantarum* 2362, approximately 400 million lactobacteria in one dose („Medipharm" Kågeröd, Sweden).

Patients included into Group III received standard enteral feeding formulas supplemented with only those fibres that have been mentioned above.

Visually synbiotic/prebiotic is colourless powder. Immunmodulating blends have been prepared according to the scheme:

- 100 mL Nutrison Standart
- 200 mL drinking water
- 1 package of synbiotics/blend containing prebiotic (15 g)

Ingredients of the blend have been mixed together with the help of blender.

Picture 2. Preparation of enteral feeds.

The blends have been administered in groups orally, only in separate exceptional occasions after the surgery via enteral feeding probe, which has been inserted in the

proximal part of small intestine. When patients tolerated initial feeding well synbiotics/prebiotics have been added to natural yoghurt (Bio Lacto). This blend has been prescribed twice a day. Upon the clinical feeding tolerance patients have been divided in three groups:

- Good tolerability – blend is tolerated well no complaints about meteorism and nausea has been observed, the speed of blend administration on average 50ml/h.
- Mild intolerability – patients have noticed meteorism, mild nausea, speed of blend administration on average 30 ml/h.
- Poor tolerability – the administration of blend due to nausea, severe meteorism, increased IAP has to be discontinued, however, later after decrease of obstacles limiting the feeding, the process of feeding could have been fully completed.

After the end of the study answers from the manufacturer have been received and the double blind code has been broken, thus making the contents of blends received by each patient group known.

The studies on prebiotics and synbiotics have been made and are currently being made in several clinics of Europe and in the world; nevertheless, our study is unique due to the fact that until this moment there have not been published any data on early peroral application of prebiotics and synbiotics in patients suffering SAP. The scientific consultant of the research is Professor Stig Bengmark (Sweden), who is the leading world researcher in the field of prebiotic and synbiotic therapy. The raw materials used in the research were delivered for free of charge by the company "Medipharm" Kågeröd in Sweden; the organizers of the study do not have any legal and economic liabilities towards this company. The patients did not have to purchase the supplements: prebiotics and synbiotics; they were provided for free of charge. The author of the dissertation has not received any material compensation from the above mentioned company before the study, neither during the study nor after the study. The clinical study has not been sponsored by any pharmaceutical companies.

The study has been performed in compliance with the regulations from the declaration of Helsinki and human rights convention; the authorization for the study has been received from the local Ethical Committee of the hospital and the Ethical Committee of RSU. Patient randomization in groups has been done by the help of independent expert. The study personnel have not been informed on the contents of the blend and do not know which preparation the patients have been given. The preparations do not differ neither due to their taste or smell nor visually.

Statistic data analysis has been done by comparing the groups among themselves in the following manner: Group I/Group II, Group II/Group III and Group I/Group III. Statistic data analysis has been done using SPSS version 11.0. All data have been transferred to average values ± standard deviations (SD).

7. RESULTS

7.1. PATIENT GROUP CHARACTERISTICS AND ETHIOLOGY

90 patients with severe acute pancreatitis have been included into the randomized, double blind, prospective study. 32 patients have been included into the Group I, 30 in Group II and 28 in Group III. Proportion of males and females in the population of the study has been 1:1.7, more detailed demographic indicators see in Table 1.

Table 1.

Group characteristics and demographic data.

	Group I		**Group II**		**Group III**	
	n	SD	n	SD	n	SD
Patients	32	-	30	-	28	-
Male	22	-	20	-	19	-
Female	10	-	10	-	9	-
Age	51.8	17	45.4	11.7	43.8	16.4

Groups were statistically comparable among themselves by age, sex and demographic data. Main severe acute pancreatitis etiologic factors have been alcohol and gallstone disease. Gallstone disease prevailed among females as a reason for development of severe acute pancreatitis, however for males the main factor has been alcohol intake. The experience from the last year and a half shows that the number of patients for whom severe dyslipidaemia (hypertrigliceridaemia) and/or metabolic syndrome has been the reason for acute pancreatitis increases. Etiological factors have been arranged into Table 2.

Table 2.

Etiological factors of SAP.

	Group I (n=32)	**Group II (n=30)**	**Group III (n=28)**
Alcohol	14	18	16
Gall stones	10	7	7
Other*	8	5	5

** Mostly dyslipidaemia and/or metabolic syndrome.*

7.2. SEVERITY OF THE DISEASE AND COMPLICATIONS

On admission the severity of disease (APACHE II) among the groups does not differ statistically. Clinical course of the disease characterised with statistically similar incidence of SIRS and MODS. Application of continuous veno-venous haemofiltration as invasive manipulation among the groups does not differ statistically. Main indications for the initiation of renal replacement therapy have been worsening of the patient's general condition, early MODS and rapid increase of intra-abdominal pressure despite complex intensive therapy within the first 24-48 hours after hospitalization. Parameters characterising the severity of disease have been summarized in Table 3.

Table 3.

Clinical course of the disease.

	Group I (n=32)		Group II (n=30)		Group III (=28)	
	n	SD	n	SD	n	SD
APACHE II (points)	6.8	4.3	8.8	3.6	8.6	4.9
SIRS	31	-	30	-	28	-
MODS	32	-	27	-	24	-
Necrotizing SAP (No:/%)	24 (75%)	-	16 (53.3%)	-	11 (39.3%)	-
Edematous SAP	8	-	14	-	17	-
CVVH	23	-	16	-	15	-

Development of multiorgan dysfunction syndrome has been very rapid and signs of initial organ dysfunction could have been observed in all patients upon admission. By administration of early complex intensive therapy rapid regression of organ dysfunction syndrome has been reached. Therefore early organ dysfunction syndrome related lethality has not been observed in the population of our study (Table 4).

Table 4.

Dynamics and consequences of MODS.

	Group I (n=32)		Group II (n=30)		Group III (n=28)	
	n	SD	n	SD	n	SD
Onset of MODS (days after admission)	0.9	1.1	0.66	0.8	0.54	1.2
MODS duration (days)	7.6	6.1	4.8	3.6	5.5	4.8
MODS first 24 h after admission (patients)	23	-	27	-	22	-
Early mortality	0	-	0	-	0	-

Upon evaluation of organ dysfunction syndrome and analysing each organ system separately, in Group II patients statistically more cases of renal dysfunction within the

early MODS has been observed versus Group I, p=0.02. On the contrary, the number of pneumonia and number of cardiovascular insufficiencies has been comparatively statistically less often observed in Group III patients versus Group I (7/16 against 0/6 cases), p=0.03 and p=0.01, respectively. Incidence of pulmonary complications did not differ among the groups and ventilatory support was needed only in 14 cases when severe intraabdominal compartment syndrome was present and after the operation. Number of other organ system dysfunctions and number of pulmonary complications among the groups do not differ statistically; these data have been summarized in Table 5.

Table 5.

Incidence of MODS and pulmonary complications among the groups.

	Group I (n=32)	**p**	**Group II (n=30)**	**p**	**Group III (n=28)**
	n		n		n
Liver disf.	17	NS	20	NS	16
Renal disf.	7	0.02	17	NS	11
Metabolic disf.	11	NS	12	NS	7
CNS disf.	16	NS	11	NS	12
Haematologic	18	NS	16	NS	16
Cardiovascular	6	NS	4	NS	0
Pulmonary*	22	NS	19	NS	16
Pleural exudates	20	NS	13	NS	12
Pneumonia	16	NS	9	NS	7
Atelectasis	2	NS	5	NS	3
ARDS	2	NS	2	NS	1
Compartment syndrome	7	<0.005	19	<0.005**	20

** Only 14 patients have been managed with ventilatory support in any stage of the disease.*

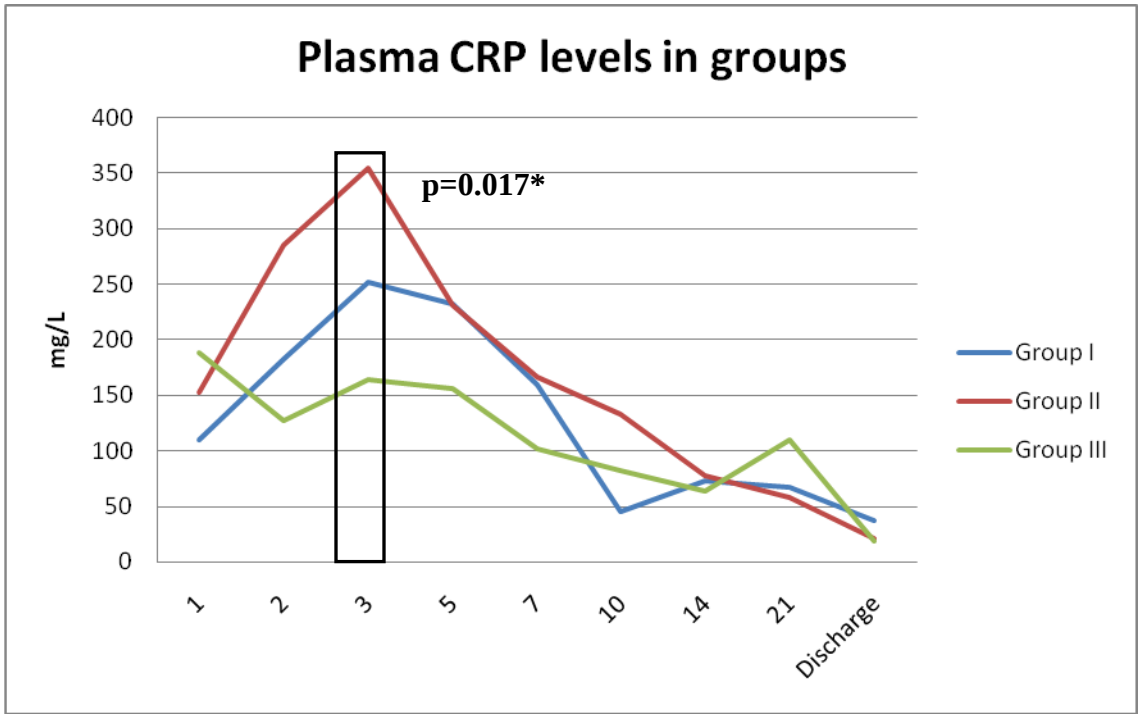
*** In comparison with Group I.*

Development of early intra-abdominal compartment syndrome more often has been observed in Group II and III (19 and 20 cases), which relates to the fact that, unlike the standard enteral feeding formulas, additives of synbiotics/prebiotics have been well tolerated even when IAP was increased. Despite the fact that increased IAP influences the possibility of enteral feeding, in most cases it has not been the cause for discontinuation of enteral feeding or diminishing of its volume.

32 Group I, 23 Group II and 22 patients of Group III have received antibacterial therapy. The average duration of antibacterial therapy in groups has been 9.7 ± 9.5 days. Most patients have received antibacterial therapy early starting from the moment of hospitalization. Correction of antibacterial therapy has been done upon the clinical situation or upon receipt of the positive bacterial culture.

Absolutely lower C-reactive protein plasma levels have been observed in Group III patients (Picture 3). Clinically observed and in literature described peak of CRP in the third day has not been observed and these levels differed statistically, p=0.017.

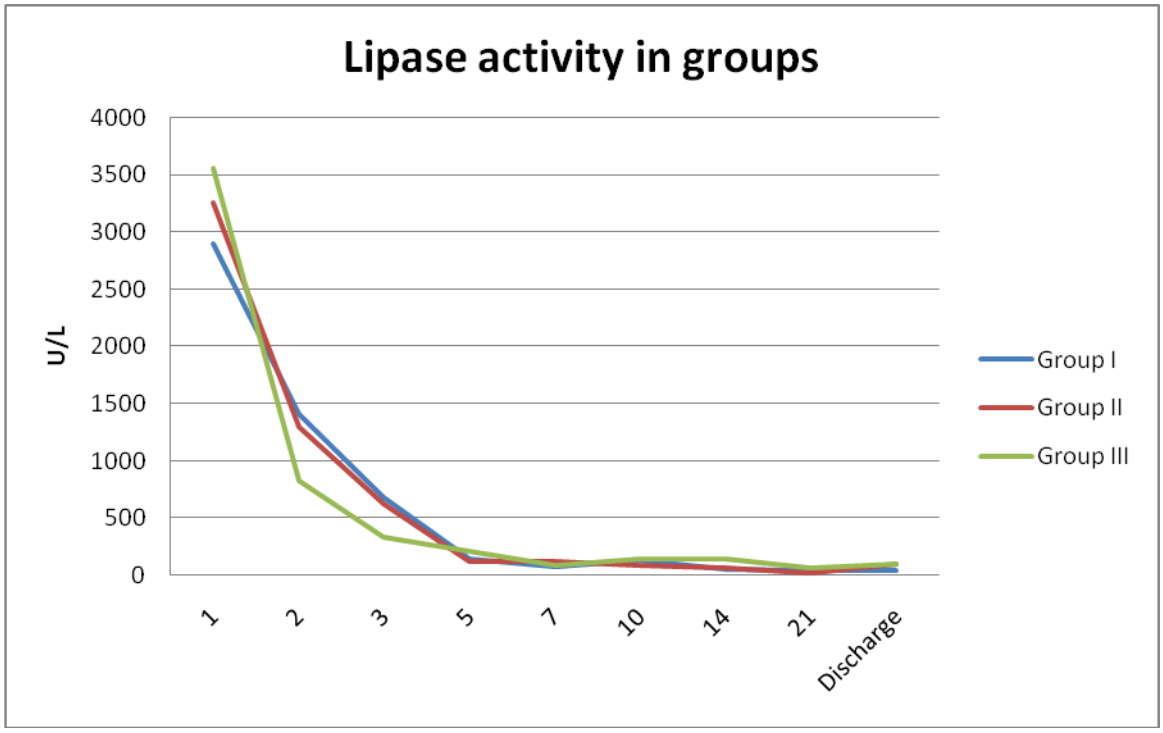
Picture 3. Plasma CRP levels in groups.



**Difference comparing Group II and Group III*

Lipase activity did not differ among the groups (Picture 4) and initiation of feeding did not cause increased plasma lipase activity. Therefore it can be stated that synbiotic/prebiotic blends do not cause increased exocrine activity of pancreas and their administration is safe.

Picture 4. Lipase activity in groups.



7.3. ENTERAL FEEDING

Initiation of early enteral feeding has been a target in all the patient groups, however possibilities for its wholesome maintenance differed from group to group. Generally all patients received early enteral feeding. It is a routine principle of feeing formula provision to which our clinic is carries out for 4 years already. In all cases when patients could start to sip water it has been possible to initiate early enteral feeding. Probes have been used for ensuring of enteral feeding rarely. It has been statistically possible to initiate enteral feeding earlier in the group of patients receiving synbiotics/prebiotics.

Statistically significant differed average administered volumes of blends as well as number of calories between Groups I/II and I/III. We have not followed the principle to ensure average necessary number of calories per day for the intensive care patients. Much more important is a principle to feed the gut, thus improving the gut barrier, diminishing signs of inflammation response and possibilities for bacterial translocation. This principle hypothetically is the basis for the lowering of numbers of infectious complication in case of necrotizing pancreatitis. Comparing feeding parameters of Group II and III statistically significant differences have not been observed. Parameters of enteral feeding have been summarized in Table 6.

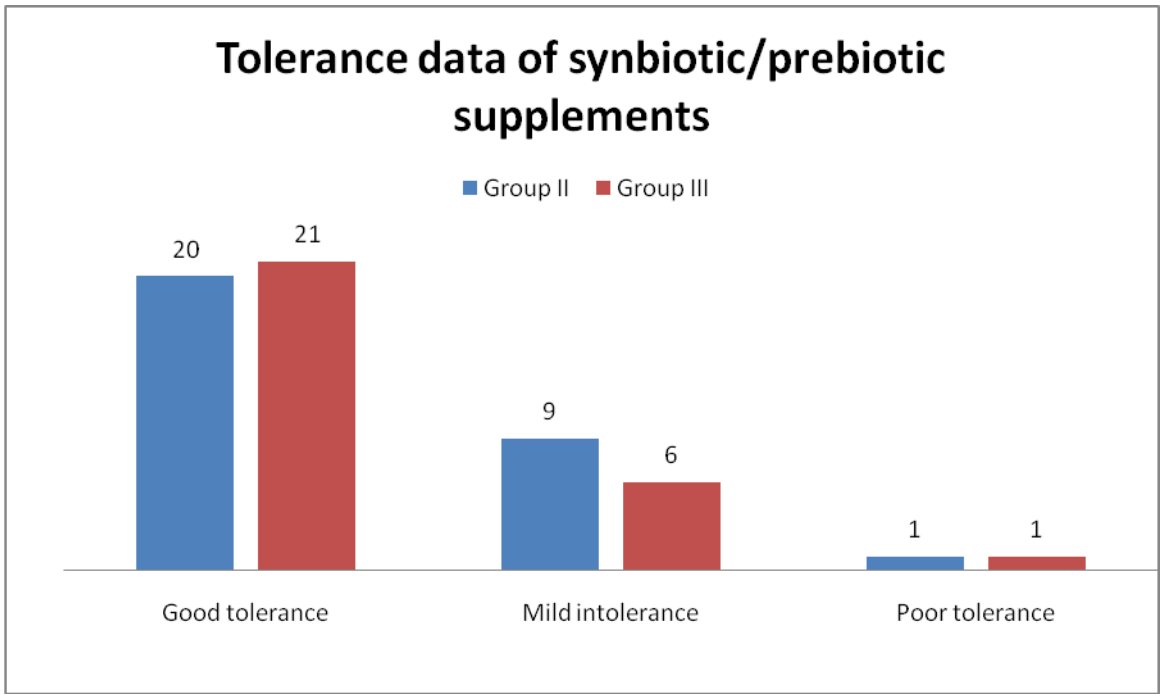
Table 6.

Enteral feeding protocol and calories.

	Group II (n=30)	**p**	**Group I (n=32)**	**p**	**Group III (n=28)**
	n		n		n
EN after admission (days)	2.3 ± 1.5	0.05	4 ± 2.3	0.01	1.8 ± 1.2
Duration of EN (days)	8 ± 1.8	NS	9.4 ± 12.5	NS	7.6 ± 1.5
Average volume in 24 h (ml)	100.2 ± 126.5	0.001	384 ± 289	0.001	100.1 ± 119
Calories (kcal)	100.2 ± 126.5	0.001	384 ± 289	0.001	100.1 ± 119
Formula sachets	12.8 ± 3	-	-	-	12.8 ± 2.9

The largest number of patients tolerated enteral feeding well, only in separate cases there have been a necessity to discontinue the initiated feeding or diminish the volume of formulas administered (Picture 5).

Picture 5. Tolerance of synbiotic/prebiotic supplements.



After initial successful enteral feeding we increased gradually volume of feeding formulas, additionally oatmeal soup and bio-lacto yoghurt has been added. On average after a week from the start of the disease patients tolerated standard hospital food well and administration of standard enteral feeding formula has been stopped.

7.4. SURGICAL ACTIVITY AND INFECTION DATA

Quite high surgical activity has been observed in Group I comprising 37.5%, however in Group II and III it has comprised only 10% and 7.2%. The main indications for surgical therapy have been suspected peripancreatic infection, progressing intra-abdominal compartment syndrome, rapid worsening of general condition despite the complex therapy and obscure diagnosis at the admission. During the surgery lesser sac has been opened, mobilization of pancreas and digital necrosectomy within the boundaries of possibly vial tissues was performed, in cases of necessity lumbotomies of right and left sides have been performed. After adequate drainage of retroperitoneal space and abdominal cavity, the abdomen was closed using semi open technique performing lesser

sac partial laparostomy to avoid the development of intra-abdominal compartment syndrome. Principle of limited laparotomies has been used for the patients undergoing surgery during the last years. Infected necrosis or infected fluid collections has been pointedly drained via extraperitoneal root under control of presurgical CT or US scan thus avoiding opening free abdominal cavity. Statistically significant differences in synbiotic/prebiotic groups have been noticed comparing the frequency of peripancreatic infection. Statistically larger surgical activity in Group I resulted in a larger number of peripancreatic infections and in significantly higher frequency in the development of septic complications. Frequency of primary infection among the groups has not reached statistically significant difference, although the primary infection indicators within the groups have been very low (Table 7).

Table 7.

Surgical activity and infection data.

	Group II (n=30)	**p**	**Group I (n=32)**	**p**	**Group III (n=28)**
	n		n		n
Operations	3	0.01	12	0.01	2
Primary infection	0	NS	3	NS	2
Secondary infection	2	0.03	9	0.001	0
Septicaemia	2	0.05	7	0.05	2
Severe sepsis	2	NS	1	NS	2
Septic shock	2	NS	1	NS	0

7.5. OUTCOMES AND LETHALITY

Statistically significant differences have been observed among the groups considering overall hospital and ICU stay. Significantly shorter hospital and ICU stay was observed

in Groups II and III comparing to Group I. Average number of days spent in intensive care department does not differ in Group II and III (Table 8).

Table 8.

Outcomes and mortality.

	Group II (n=32)	**p**	**Group I (n=30)**	**p**	**Group III (n=28)**
	n		n		n
Hospital stay (days)	22.5 ± 25	0.03	36.3 ± 35	0.02	19.8 ± 15.3
ICU days	7.9 ± 11.6	0.05	16.3 ± 25	NS	8.4 ± 12.8
Mortality (%)	0	0.02	16.7	NS	3.6

Most important differences among the groups were observed comparing mortality. Overall lethality in Group I was 16.7%, that corresponds to the data from the large SAP observatory study data from the literature. But we can point out that mortality in patient groups receiving synbiotic/prebiotic supplements was significantly low. There were no lethal outcomes in Group II and in Group III overall lethality was only 3.6%. Our data statistically prove effectiveness of synbiotic/prebiotic supplements and further clinical studies are justified.

8. DISCUSSION

8.1. PATIENT GROUP CHARACTERISTICS AND ETHIOLOGY

Still severe acute pancreatitis is a serious problem for surgeons working in intensive care and ICU specialists. Clinical signs and course of SAP have remained practically the same, significant changes in therapeutic strategy have influenced outcomes but they are still not satisfactory. Currently published statistical data indicate that there is a tendency for the cases of severe acute pancreatitis in population to increase. It can be explained

with increased incidences of gallstone disease. Alcohol consumption indicators and numbers of alcohol abusers increases every year. Experience from the United States indicates the importance of obesity and lipid metabolism disturbances (hypertrigliceridaemia) in the development of acute pancreatitis. All these significant risk factors can be encountered among individuals living in Latvia. Alcohol and gallstone disease has been the main aetiological reasons for acute pancreatitis for the patients included in our study, which corresponds with experience of other European countries.

8.2. SEVERITY OF THE DISEASE AND COMPLICATIONS

The prediction of the severity of the disease is very important in order to choose an adequate therapeutic strategy. Within the framework of the study the APACHE II score was applied for the estimation of physiological changes of the patient's metabolism during the first 24 hours from the hospitalization. The indicators describing the severity of patients' general condition were similar in the groups. APACHE II scores were appointed to all patients only at the moment of their admitting into hospital, in our opinion, it is the most objective indicator for prediction of the severity of the disease. The total APACHE II point scores differed (was smaller) from the data indicated in the publications of the other authors, however, the fact should be taken into consideration that all SAP patients soon after their admission into hospital were stationed in ICU and the organ support therapy was started in timely manner. Timely application of complex organ support therapy notably permits to modulate the physiological response of the organism and does not allow deep changes in the vital and biochemical indexes, which determines the sum of APACHE II scores.

Severe clinical forms of acute pancreatitis mainly are linked with the development of necrosis in gland and peripancreatic tissues, which appears during the first four days as from the onset of the disease. Appearance of necrotic forms prevailed equally in all three study. There were a little more cases of edematous pancreatitis observed in the group of patients who had been treated with prebiotics, though these data did not show statistically

significant difference and did not leave an impact on the final outcome of the treatment. Similar MODS incidence was observed in all groups; it proves the fact that the clinical pace of severe acute pancreatitis is not determined by the amount of necrosis in early stages, but the response of the organism to inflammation in the forms of SIRS and MODS. An early and adequate therapy is the decisive factor in such cases. It is of great importance to recognize the patients with clinical symptoms that might indicate on unfavorable clinical forms. Some of the aforementioned symptoms indicating on unfavorable clinical presentation of the disease in patients at the age of > 60 are the following: pleural exudate, overwhelming SIRS, cognition disorders and elevated blood urea nitrogen. Some other authors mention the following criteria as the indicators for prediction of unfavorable clinical forms: pulmonary dysfunction, pulmonary complications and cardiovascular insufficiency. In many situations the decisive role is played by timely recognition of the aforementioned symptoms and their prevention, which is the most important aspect for positive outcome. In case of the patients who were treated with the supplements of prebiotics, in early stages lower incidence of cardiovascular deficiency and pneumonia was observed. It is related to the ability of prebiotics to modulate the inflammatory response, which determines development of systemic complications. The differences in the dysfunction of the other organs did not reach statistically significant threshold; however, they were prevailing in the control group. The aforementioned proves the fact that prebiotics and synbiotics are capable of modeling the inflammatory response and in the future there is the necessity to continue the study by involving larger number of the patients, in order to prove the above mentioned hypothesis.

The increased vascular permeability cause pronounced haemoconcentration. Sequestration, of liquid rich exudate in the abdominal cavity, retroperitoneal space and in the mesenteric root followed by intestinal oedema is typical in SAP patients. Intra-abdominal pressure is increasing rapidly after the increase of retroperitoneal oedema. Increase of intra-abdominal pressure above 12 mmHg impacts perfusion of all intra-abdominally and retroperitoneally located organs. Microcirculation of gastrointestinal

tract is greatly disturbed in cases when intra-abdominal pressure is elevated above 20 mmHg. In cases when intra-abdominal pressure increases permanently enteral feeding cannot be ensured. Control of intra-abdominal pressure is a standard in our clinic. Regardless to the fact that in the group of synbiotics initially there have been more patients with elevated intra-abdominal pressure, enteral nutrition has been successful. Even patients with intra-abdominal pressure raging from 12 to 15 mmHg have tolerated enteral nutrition well. It could indicate better restitution of gastrointestinal tract function and fact that intra-abdominal hypertension is not the only factor that precludes initiation of early enteral feeding. Early enteral nutrition was possible even for the patients with intra-abdominal hypertension and intra-abdominal compartment syndrome and the nutrition was well-tolerated by the patients. The use of synbiotic/prebiotic renewed the function of alimentary tract much faster; the result of it was a considerable decrease in the number of infectious complications.

The renewal of alimentary tract function, the decrease of SIRS signs and the regress of organ dysfunction permit to make indirect conclusions about the dynamics of inflammatory response. Changes in plasma acute inflammatory phase proteins describe the dynamics of inflammatory process. CRP should be mentioned as one of the markers of systemic inflammatory response. C-reactive protein is synthesized in liver and the maximum concentration of plasma is reached on the third day after the beginning of the illness. At the beginning of inflammatory response there are many cytokines and interleukins developed that determine the synthesis of TNF-α, which, in turn, provides the signals for the synthesis of CRP. Within the framework of our research CRP was defined as the marker of the inflammatory response. Unexpectedly there was observed a phenomenon which had not been published in clinical studies earlier: a statistically credible “peak” of plasma CRP concentration that appeared in the group of synbiotic therapy on the third day after admitting the patient into hospital. There was no third day CRP “peak” observed in the group of patients treated with prebiotics. The increase of protein plasma CRP concentration in acute phases in the group of synbiotics therapy indicate on possible activation of proinflammatory phases; it has been described in the

study with animals by using a special immune-modeling formula, however it was done without the addition of synbiotics. It is possible to assume on the bases of the aforementioned that the supplement of synbiotics stimulates MALT and GALT systems that are situated in the alimentary tract, which indirectly proves that the immune system of the alimentary tract has renewed. It should be noted that SIRS reaction did not progress in the group of patients who were treated with synbiotics and there was observed a statistically important decrease in the number of pulmonary and cardio-vascular complications despite the third day peak of plasma CRP. The aforementioned proves the hypothesis that enteral nutrition supplementing with specific substances that modulate the immune system can have positive influence on systemic inflammatory response and the final outcomes of the disease.

8.3. TREATMENT

International, European and guidelines from USA incorporated with our experience has been the base for the development of therapeutic strategy for severe acute pancreatitis.

Initial evaluation of the patient general status has been performed in admission room with surgeon and ICU specialist involved. The most severe patients with signs of initial organ dysfunction have been hospitalized directly in ICU for early (first 24-48 hours after admission) organ support therapy. Such experience is recommended by internationally gathered results. First 48-72 hours from the onset of the disease are very significant and this period is called therapeutic window, period when it is still possible effectively modulate inflammatory response in its initial stage. Timely, early fluid replacement and organ support therapy in ICU that is based on the principles of isovolemic haemodilution improve microcirculation and organ perfusion. Since the year 1999 continuous veno-venous haemofiltration has been implemented as additional method of treatment of the patients suffering SAP in our clinic. At the moment treatment experience with application of CVVH for more than 150 SAP patients has been collected. Considering international publication data CVVH is used to modulate inflammatory response and eliminate

cytokines from circulation, therefore diminishing undesirable pathophysiologic effects. This fact is very important in proinflammatory stage of inflammation (SIRS) as well as in anti-inflammatory (CARS - compensatory anti-inflammatory response syndrome) stage to balance the inflammatory response. By application of this method, mediators of inflammation are mainly eliminated from blood stream and in lesser extent from interstitial compartment. Some authors consider that cytokine elimination from interstitial compartment has more significant role than their elimination from blood circulation. This is called Honore principle - the mediators of inflammation are blocked in area where they do harm. By balancing of inflammation mediator activity in the intracellular space the damage of tissue can be significantly diminished and MODS can be prevented. Only slow flow CVVH is used in our clinic at the moment, which differs from the experience of authors from China. Application of high-speed flow filtration larger amount of blood is filtrated in one unit of time, however this method of therapy cannot be used for a long time. Whereas slow flow filtration can be used for a long time and thus the total amount of blood filtrated will not differ significantly.

Despite results of recent year publications that do not recommend application of antibacterial therapy, the majority of our patients have received initial antibacterial prophylaxis with fluorochinolons/metronidosol or imipenem/cilastin. The main task of antibacterial therapy is a prophylaxis of septic complications. However, for the moment there are no powerful proofs that the administration of antibacterial agents significantly diminishes possibility of development of septic complications. Continuous veno-venous haemofiltration has been applied in the initial stage of treatment to the majority of patients for ensuring of homeostasis and circulation. By application of this method not only cytokines but also pharmacological substances including antibacterials are eliminated from the organism. Average administered dose of fluorochinolon reached 200 mg twice a day which could result in insignificant prophylactic effect for the patients receiving CVVH. Routine administration of antibacterial agents in patients with SAP has not proven its efficacy. On the contrary in many cases it is even unacceptable. Therefore selective administration of antibacterial prophylaxis is very important in risk groups. This

approach allows to minimise the number of patients receiving antibacterial therapy. Our study for the last year shows that synbiotic/prebiotic administration allows to reduce prophylactic antibacterial therapy.

8.4. ENTERAL FEEDING

Despite the existing numerous proofs witch confirm advantages of enteral feeding over parenteral feeding in patients with SAP the discussion is still actual how to ensure appropriate enteral feeding. The questions about the content of enteral nutrition formulas, roots of administration are also important, but the most important question, which cannot be answered unambiguously, is a question about ensuring of gut barrier function. Dubious is application of parenteral feeding in cases when enteral feeding can be ensured when clinical course is complicated by peripancreatic infection and surgery following it.

Adding different kind of additives and synbiotics to standard enteral nutrition immunomodulatory effects increase significantly. On this concept principle of synbiotic supplementation is based. Synbiotics/prebiotics contain fibres and bacteria, which can colonize human gastrointestinal tract. It is possible to ensure maximum desirable positive effect from enteral feeding by dosed administration of enteral nutrition formulas mixed with special immunomodulating agents.

International enteral nutrition guidelines recommend to initiate enteral feeding as soon as possible. Taking into consideration these recommendations, conscious, haemodinamically stable patients that were able to sip water were enrolled in study. Initially small test doses of enteral feeds were prescribed. If no discomfort or gastric evacuation disturbances were observed feeding rate have been gradually increased to 30 ml every 1.5 to 2 hours. The same proportion has been followed in the groups of synbiotics/prebiotics. This regimen of feeding has been well tolerated by the majority of patients. After gradual collection of material we could conclude that even patients with necrotic pancreatitis with parallel renal replacement therapy tolerate the feeding well. Similar observations have already been mentioned in several studies where patients tolerated intragastral feeding via probe well. The authors of the studies have observed no

clinical worsening and no serious laboratory data abnormalities by early administration of feeding formula into the stomach that correspond with our results.

At the moment more and more authors support the principle to infuse nutrients into the gastrointestinal tract without reaching the level of necessary caloric supply for the day. This principle is a basis for ensuring the integrity of gastrointestinal tract. Even in cases when it has not been possible to ensure goal feeding we have observed better clinical course and less complication rate. Experience shows that early oral feeding even in cases of severe clinical forms is possible and there are no negative effects on clinical course and final results from adding synbiotics to feeding protocol. In the majority of cases to reach and strictly keep to principle of goal feeding is not even possible and therefore issue about importance of caloric supply in the initial stage of treatment is under discussion. Statistically significant differences have been observed among the groups in the volumes of formulas administered in 24 hours and in caloric supply as well as in development of infectious complications. Therefore we are keeping to principle "to feed the gut" and not to ensure all daily necessary calories with the enteral feeding. Small dose enteral feeding improves metabolism of gastrointestinal tract epithelium, ensure effective function of mucous membrane that very significantly improves barrier function. The main task of early enteral synbiotic/prebiotic administration as we think is to ensure the locally necessary nutrients to the mucous membrane, increase perfusion and to stimulate transit of the gastrointestinal tract. Ensuring of early, adequate (in terms of amount and caloric supply) enteral feeding is the best way how to early treat and prevent rapid organ dysfunction and to maintain integrity of gastrointestinal tract. Analysing the data received during the study term 100 ml of symbiotic/prebiotics supplements (on average 100 kcal) administered daily cannot be considered as an adequate enteral feeding in a traditionally accepted way. At the moment we can speak about dosed immunomodulating substance input into the gastrointestinal tract to remarkably improve gut barrier and stimulate transit function. We think that these two obstacles are the most important for the SAP patients.

One of the most important factors influencing start and appropriate commencement of enteral feeding is intraabdominal pressure. We have observed that enteral feeding is not

possible when intraabdominal pressure is elevated markedly. Increased intra-abdominal pressure has been contraindication for ensuring of adequate feeding in patients receiving standard enteral feeding formulas. Tolerance results of standard enteral nutrition formulas are directly proportional to intra-abdominal hypertension. The higher pressure the lesser is possibility to start adequate enteral feeding and lower tolerance rates of feeding formulas. Even in cases when IAP reached 12 to 15 mmHg Synbiotic/prebiotic supplements were tolerated well and no clinically negative consequences were observed. This observation can be partially explained by the fact that restoration of gastrointestinal tract function was more rapid in patients receiving Synbiotic/prebiotic supplements and that increased intraabdominal pressure is not the only limitation for early application of enteral feeding. Small volumes of blends allowed us to start feeding protocol as early as possible and elevated intraabdominal pressure was not contraindication. This observation can widen application of Synbiotics/prebiotics in everyday clinical practice.

Very important argument against early enteral nutrition in patients suffering SAP is stimulation of exocrine function and stimulation of autodigestive processes in gland. Plasma lipase activity is one of the most important parameters characterising exocrine function and describing local inflammation process. Clinically significant elevation of plasma lipase activity was not observed in patients receiving Synbiotics/prebiotics, this proves that application of these substances in enteral nutrition scheme is rational and safe.

8.5. SURGICAL ACTIVITY AND INFECTION DATA

Severe acute pancreatitis has two-phase clinical course. In the initial stage (during first two weeks) both the prognosis for the patient and the final outcome of the treatment are determined by systemic inflammatory response and early multi-organ dysfunction. Both infection abutting and the complications related to it are the main risk factors that determine the further pace of the disease and the forecast for the later stages (starting with the 2^{nd} week). Consequently, the ways how to reduce the frequency of necrosis infection are very important. Currently there are the results of large multi-centre results

published that have not proven the importance of anti-bacterial therapy in the decrease of infectious complications. It has been proven in statistically credible way that the enteral nutrition reduces the frequency of infection, however, the total results are still not satisfactory. The infectious complications determine the lethality in later stages, which in case of infected necrosis reach even 50%. The above mentioned proves that there is the necessity to continue searching for new methods the application of which decreases the possibilities of infected necrosis in much more effective way. Gut barrier plays the most important role in the development of infected necrosis. One of SIRS consequences is the dysfunction of intestinal tract, which becomes apparent as inability to tolerate enteral nutrition and the loss of gut barrier function. In the result of bacteria translocation it gets into mesentery lymph glands, and then disseminates into reticulo-endothelial system and finally reaches the blood flow. It becomes clinically apparent as peripancreatic infection and sepsis. If from the second week of the illness there is observed a repeated SIRS reaction and MODS for a patient, it indirectly indicates on abutting the infection.

The other essential factor that opens the way for the infection is early surgical intervention. Early surgical activity cannot be allowed even in the cases of necrotic forms. During early surgical intervention and the drainage of peripancreatic fluid collections there is the way opened for nosocomial infection; it is associated with the drains and usually appears approximately on the fourth day after the surgery. It is confirmed by our data that the therapy of synbiotics/prebiotics is clinically effective method for preventing infection, which is proved by statistically significant decrease in the number of infection cases, the necessity for early surgeries and also the decrease in the total number of surgeries in group of synbiotics/prebiotics. Conversely, the large number of early and total surgical activities in the control group is linked with the explicit, uncontrolled SIRS arising due to the lack of conservative therapy efficiency and larger number of infections.

Due to the fact that the surgical activity was considerably smaller in the groups of synbiotics/prebiotics, there were also less secondary infections observed; however, the most important fact is that enteral nutrition prevented the generalization of the infection

and the development of septicaemia even in the cases of infected necrosis. The incidence of primary infections did not show statistically important difference and was small for all groups of patients. Even in cases of infected necrosis it was possible to continue the nutrition after surgery according to the previous schedule and there did not develop repeated dysfunction of alimentary tract. SIRS modeling and strengthening of the gut barrier function in the early stages resulted as the decrease in the frequency of infection and the smaller necessity for surgical activities later.

The fact that there are a smaller number of complications and necrosis infection in the group of synbiotics indirectly indicates on the ability of synbiotics therapy to module the inflammatory response.

8.6. OUTCOMES AND LETHALITY

Severe acute pancreatitis is a disease which has a very complex clinical course and there are many specialists involved in the treatment process. The costs of treatment are considerable, especially in the cases of infected necrosis, when the patients are obliged to stay in a hospital for long period of time (including ICU), and often there is the necessity for repeated surgical interventions. As it has been already mentioned above, timely recognition of severe necrotic forms of disease and early conservative therapy have essential meaning in the further course of the disease. Enteral nutrition is a very important part in the complex severe acute pancreatitis therapy protocol.

It is really important not to allow a considerable progress of SIRS and the development of MODS in early stages of the disease. A decisive role is played by the renewal of intestinal tract function and gut barrier, as well as the renewal of transit function of intestinal tract. Early renewal of intestinal tract functions considerably decreases the possibility of the development of intra-abdominal hypertension. Uncomplicated clinical course at the initial stage considerably decreases the possibility that there will be infectious complications at the later stages. There was statistically less cardio-vascular complications and the development of pneumonia observed in the group of patients who had been treated by synbiotics/prebiotics, as well as there were less cases when surgical

intervention was necessary. The maintained function of intestinal tract prevented the generalization of the infection and the development of septicaemia even in the cases of infected necrosis.

The traditional indicators of treatment efficiency are the following: the number of days spent in ICU, the overall hospital stay and the lethality. It should be noted that these indicators were comparatively small for all groups of patients, however, the best treatment results were observed in patients, whose enteral nutrition schedule was supplemented by synbiotics/prebiotics. Due to the small number of early complications and late septic complications, there was a considerable decrease in the length of treatment in ICU and overall hospital stay. The small frequency of infected necrosis and consequently low surgical activity considerably decreased the possibilities of developing the complications that are related to the surgery (fistulas of alimentary tract and pancreas, bleeding from retroperitoneal space, development of hernias after the surgery).

Within the group of patients involved in the study there was a possibility to avert early lethality completely due to the application of early complex ICU therapy, as well as the early lethality associated with fulminant MODS. In later stages the lethality was determined by the infection, but also then the total lethality indicators for all groups of patients were very small. The fact should be noted that we did not observe any lethal outcome in the group of patients who received early synbiotics therapy. Such fact had never been mentioned earlier in the publications of the other authors. This study proves the advantages of synbiotics application for the patients with severe acute pancreatitis.

9. CONCLUSIONS

1. Low caloric supply, small volume immunomodulating substance addition to early standard enteral nutrition formulas is rational and safe in patients with severe acute pancreatitis. It significantly diminishes duration of hospitalization, risk of the development of infectious complications and lethality;
2. Patients tolerate synbiotic additives well despite intra-abdominal hypertension;

3. Improvement of gut barrier function in the symbiotic/prebiotics group gives hope that this therapy could be applied also in treatment of other acute and chronic surgical pathologies (intra-abdominal infection, sepsis, inflammatory bowel disease etc.);
4. Application of symbiotic/prebiotic formulas lowers need for surgical intervention and significantly reduces number of secondary infections;
5. Number of infectious complications has diminished significantly with application of this type of therapy. However, more data must be collected to evaluate the advantages of this method.
6. Dosed nutritional substance administration in order not to overload gastrointestinal tract and not to cause difficult to control abnormalities in the physiology of crisis seems more rational at the moment.
7. It is necessary to perform more randomized, double blind, prospective, multi-centre studies to strictly statistically prove the significance of synbiotics in modelling of inflammatory response and diminishing of septic complications.

10. PRACTICAL INPUT OF STUDY AUTHOR

1. The author of the study has personally performed the treatment of all patients involved in this study, except for the ICU stage, when the treatment was coordinated with ICU specialists.
2. The intraabdominal pressure of the patients was monitored every day (2 times per day as the minimum), as well as there was ensured enteral nutrition and assessed the tolerance of the nutrition formulas.
3. The author of the study has personally performed the primary and repeated (if there were any indications) surgery of all patients included in the protocol, as well as ensured the wound care during the post-surgery period.
4. The author of the study has personally compiled all results and has entered them into the developed account system of the patient data.

5. The author of the study has personally performed the analyses of all clinical and laboratory data, as well as their statistic analysis and interpretation.
6. The author of the study in cooperation with the scientific consultant of the research has prepared six thematic publications; the publications have been published in internationally recognized editions.
7. Currently the author of the study in cooperation with the colleagues continues the research in the field of treatment the patients with severe acute pancreatitis by estimating the importance of dyslipidemia in SAP development and pathogenesis, as well as by analyzing the importance and advantages of aimed limited laparotomy for the sanation of infected necrosis in comparison with the conventional methods.

11. LIST OF PUBLICATIONS ON THE STUDY THEME

1. Plaudis H, Pupelis G. Early Oral Feeding in Patients with Severe Acute Pancreatitis. Double Blind Prospective Randomised Trial. Acta Chirurgica Latviensis, 2008 (8): 48 – 54.
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12. CONFERENCE THESIS ON THE STUDY THEME

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3. Plaudis H, Purmalis G, Pupelis G. Role of Synbiotics in the management of patients with severe acute pancreatitis and surgical sepsis: A double blind randomised prospective clinical trial, preliminary report. 11th Annual Conference of European Society of Surgery 2007 thesis, p 65.
4. K.Snipe, G.Pupelis, H.Plaudis, M.Rudakovska. Increased intra-abdominal pressure, is it of any consequence in severe acute pancreatitis. 3rd World Congress on Abdominal Compartment Syndrome 2007 thesis, p 256.
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9. K.Snipe, G.Pupelis, H.Plaudis, M.Rudakovska. Increased intra-abdominal pressure, is it of any consequence in severe acute pancreatitis. 6th Congress of the European Hepato-Pancreato-Biliary Association 2005 thesis, p 66.

10. H.Plaudis, M.Rudakovska, K.Snipe, A.Grigane, G.Pupelis. Renal replacement therapy in the treatment of severe acute pancreatitis and surgical sepsis. 8th Annual Conference of European Society of Surgery 2004 thesis.

13. APPEARANCE

1. H.Plaudis, V.Boka, G.Pupelis. Early Oral Synbiotic/Prebiotic Supplements in the Treatment of Severe Acute Pancreatitis. Double Blind Prospective Randomised Trial. The 6th Meeting of the Baltic Association of Surgeons 2009. Oral presentation.
2. Pupelis G., Zeiza K., Plaudis H. Conservative approach in the management of SAP. Eight-year experience in single institution. 8th World Congress of the International Hepato-Pancreato-Biliary Association 2008. Oral presentation.
3. Plaudis H, Purmalis G, Pupelis G. Role of Synbiotics in the management of patients with severe acute pancreatitis and surgical sepsis: A double blind randomised prospective clinical trial, preliminary report. 11th Annual Conference of European Society of Surgery 2007. Oral presentation.
4. K.Snipe, G.Pupelis, H.Plaudis, M.Rudakovska. Increased intra-abdominal pressure, is it of any consequence in severe acute pancreatitis. 3rd World Congress on Abdominal Compartment Syndrome 2007. Oral presentation.
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9. K.Snipe, G.Pupelis, H.Plaudis, M.Rudakovska. Increased intra-abdominal pressure is it of any consequence in severe acute pancreatitis. 6th Congress of the European Hepato-Pancreato-Biliary Association 2005. Oral presentation.
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