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Changes in the Management of Treatment in Acute Pancreatitis Patients

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1. Introduction

Acute pancreatitis is an inflammatory condition with a variable clinical course from mild to the most severe with serious complications that attempt the life of a patient. According to the Atlanta classifications the severe acute pancreatitis occurs approximately at 25% of all patients with acute pancreatitis and it is associated with 10-20% of mortality. Death of the acute pancreatitis patients is often connected of at least one organ.

There are two phases of the severe acute pancreatitis relating to the mortality. The first phase, two weeks after onset of syndrome, is characterized by hypovolemia or even by the shock. It is accompanied by the systemic inflammatory responsive syndrome with production of inflammatory mediators and cytokines, which cause consecutive injury of lungs, livers and cardiovascular system. The multi organ failure is a very common appearance in the case of the severe acute pancreatitis and it happens very often even when the infection is absent. The second phase of this disease (third-forth week) is characterized by the complications caused by the infection of pancreatic necrosis. About 40-70% patients with necrotic acute pancreatitis is afflicted by the infection of the pancreatic necrosis, which causes the deaths of acute pancreatitis patients (Beger et al., 1997). The extent of the pancreatic necrosis and the duration of disease are the risk factors of the local pancreatic infection. Its incidence tends to culminate in third week of disease, though it may appear in whichever phase of the disease (Büchler et al., 2000). Severe acute pancreatitis requires treatment at the hospital, which is developed from personal, professional and technical point of view, where is a possibility to do the full diagnosis and therapy and the interdivisional cooperation, what is the basic presumption for treatment and diagnosis of acute pancreatitis.

Diagnosis is based upon clinical presentation, laboratory indicates and imaging studies, whilst illness severity can be assessed by clinical scoring systems, such as Ranson, Glasgow or Apache II criteria, or by radiological assessments such as the computer tomography severity index. Mild disease is often self-limiting and inflammation resolves with simple medical management. However, a minority of patients (up to 20%) will develop severe disease that carries substantial morbidity and mortality.

Over the past decades, management of severe acute pancreatitis changed from an early operative treatment to a more conservative approach. Nowadays there is clearly no more doubt that surgery is not the first choice of treatment for patients suffering from severe acute

pancreatitis. Surgical debridement is the gold standard in patients with infected pancreatic necrosis. By delaying surgery up to the third or fourth week, sufficient debridement can be achieved, resulting in low mortality and morbidity rates. Early enteral feeding is preferred over total parenteral nutrition as it results in a reduced incidence of infection, length of hospital stay and mortality.

Besides full intensive treatment of acute pancreatitis there is a non changeable role of the surgical – operational treatment. Some indications for surgical treatment are no doubtful; some of them are the subject of discussion. The documented persistent infected necrosis and abscess is clear indication for the surgical treatment. Permanent acute abdomen, especially so called intra-abdominal compartment syndrome and persistent or increasing local complications (bleeding, ileus, bleeding of gastrointestinal tract, vascular ileus and others) are also the definite indication of the surgical intervention. Many authors consider the sterile necrosis, which causes the multi organ failure and which does not react to the maximal intensive treatment more than 72 hours, as an indicator of the surgical treatment (Götzinger, 2007).

The changes in the management of the patients with severe acute pancreatitis in the last decade contributed to the decrease of mortality. The aim of this study is to evaluate progress in the management of the patients with severe acute pancreatitis, comparing two clinical groups of patients.

2. Changes in the management of treatment in acute pancreatitis patients

Despite than mortality from severe acute pancreatitis has remarkably decreased (10-20%) during the last decades, many questions remain open about the treatment of this disease. Published literature on severe acute pancreatitis was reviewed and the decision to change the management of the treatment of severe acute pancreatitis has been made, at the First Department of Surgery, University Hospital in Košice, Slovakia. The management referred to the enteral nutrition, epidural analgesia, antibiotic prophylaxis, delay surgery to the later period in the case of infected necrosis.

2.1 Enteral nutrition

Enteral nutrition fed by the three-luminal tube applied by fibroscope, checking position by the contrast X-ray exam or by enteral nutrition through jejunostomy, in the case of already operated patient.

In 1997, McClave et al. demonstrated that nasojejunal feeding is a safe and beneficial method in mild and moderate pancreatitis (McClave et al., 1997). Later on, Nakad et al. found that nasojejunal feeding is feasible in severe acute pancreatitis, too (Nakad et al., 1998). Recently, some questioned whether nasojejunal feeding is the only proper route of enteral feeding in acute pancreatitis. The main disadvantage of nasojejunal feeding that it requires an endoscopist or radiologist to place the tube in, which may cause some delay in starting early enteral feeding (Spanier et al., 2011). Piciucchi et al. have found that enteral nutrition administered by nasogastric or nasojejunal tube seems to provide equal safety, tolerability and efficacy, even if more results are necessary to validate the routine use of nasogastric tubes in severe acute pancreatitis patients (Piciucchi et al., 2010).

One of the most common complications of enteral feeding is diarrhea, which can be detected in 20–30% of all patients. Diarrhea may deteriorate volume depletion and dehydration

resulting in further weakening of the general condition of patients who are very sick anyway and usually need intensive care management. Wide-spectrum antibiotics, which are frequently used in severe acute pancreatitis, can contribute to the development of diarrhea as a significant additional factor (Whelan, 2007). It is possible that fiber enteral nutrition formulas have some preventive effect against diarrhea though (Elia et al., 2008). This observation was supported by a recently published study by Karakan et al. showed that prebiotic fiber supplementation reduced complication rate in acute pancreatitis in comparison to standard enteral solution (Karakan et al., 2007). A meta-analysis published by Petrov and Zagainov, which was based on six randomized control trials comparing enteral nutrition with parenteral nutrition, showed that enteral nutrition statistically significantly reduced the risk of hyperglycemia ($p=0.04$) as well as insulin requirement ($p=0.001$), so it is associated with better blood glucose control in severe acute pancreatitis patients (Petrov & Zagainov, 2007). The facts that enteral nutrition is most likely superior to parenteral nutrition in preventing septic complications of acute pancreatitis, it may also eliminate some complications of parenteral nutrition (catheter sepsis, pneumothorax, and thrombosis), and costs only 15% of the cost of total parenteral nutrition, make it an increasingly accepted treatment modality (Olah & Romics, 2010).

Composition of enteral formulas can be classified into three basic categories: polymeric, (semi)elemental, and immunoenhanced. While polymeric nutrient comprises non-hydrolyzed proteins, maltodextrins, oligofructosaccharides and long-chain triglycerides, (semi)elemental contains oligopeptides or amino-acids, maltodextrins, and medium and long-chain triglycerides. Theoretically, semi elemental nutrients stimulate pancreatic secretion in less extent, but enhance bowel absorption and those are tolerated better by patients than polymeric ones (Tiengou et al., 2006; Petrov et al., 2009b).

Immunoenhanced nutrients involve substrates which modulate the activity of the immune system. Various immunonutrition formulas felt in this category, such as glutamine, arginine, and omega-3 fatty acids as well as enteral nutrients supplemented by probiotics. Recently, a meta-analysis compared (semi)elemental and polymeric formulations indirectly, using 10 randomized controlled trials where parenteral nutrition was the reference treatment (Petrov et al., 2009a). The authors, however, could not demonstrate statistically significant difference with regard to tolerance of feeding, infectious complications, or mortality in between two enteral nutrition formulas ($p=0.611$). Enteral feeds with immune-enhancing ingredients such as glutamine, arginine, nucleotides, and omega-3 fatty acids that modulate the host immune and inflammatory response have recently attracted great interest (Bertolini et al., 2007). There are promising experimental studies, where supplementation of enteral feed with glutamine or omega-3 fatty acids could reduce the severity of experimental acute pancreatitis models (Foitzik et al., 2002; Rayes et al., 2009). Adding probiotics to enteral nutrients seemed to be a promising alternative for the future. In 10 of the 15 studies, probiotics significantly reduced bacterial infection rate compared to control groups. Two studies demonstrated a clear positive trend, but no statistical significance was detected (Olah & Romics, 2010). Sun et al., in a meta-analysis of four randomized controlled trials demonstrated that enteral feeding with probiotic could not reduce the infected necrosis (Sun et al., 2009). Eckerwall and Jacobson reported about timing when to resume oral feeding in patients with acute pancreatitis (Eckerwall et al., 2006; Jacobson et al., 2007). The usual criteria to initiate oral feeding are (1) absence of abdominal pain, (2) absence of nausea and vomiting, and return of appetite, and (3) absence of complications.

2.2 Antibiotics in acute pancreatitis

Infection of pancreatic necrosis by enteric bacteria is the most common cause of death in patients with necrotizing pancreatitis. Progress in the therapeutic management of this disease has led to a decrease in the mortality of patients without infection of pancreatic necrosis, which commonly is reported to range between 5% and 15% (Tenner et al., 1997). Nevertheless, mortality rates of 20%-30% are reported in patients with infected pancreatic necrosis (Büchler et al., 2000). The clinical importance of pancreatic infection has led to the idea that the prevention of infected necrosis could be a beneficial approach.

Antibiotics prophylaxis in severe acute pancreatitis has been a matter of discussion during the past years (Büchler et al., 2000; Slavin & Neoptolemos, 2001). Recent clinical studies seem to support the notion that early administration of broad-spectrum antibiotics is capable of reducing the incidence of infected pancreatic necrosis (Pederzoli et al., 1993; Golub et al., 1998; Sharma & Howden, 2001). Two randomized double-blind studies have addressed prophylactic antibiotics in patients with acute pancreatitis with prognostically severe and severe pancreatitis on imaging (Isenmann et al., 2004; Dellinger et al., 2007). These studies have failed to show any benefit from such drugs being routinely prescribed, no difference was found in the rate of pancreatic sepsis and mortality despite previous smaller non randomized studies suggesting a benefit. On the other hand, antibiotic overuse has been associated with up 30% of patients developing necrosis superinfection with Candida species which may confer a poorer prognosis (Büchler et al., 2000; Connor et al., 2004). If antimicrobials are prescribed, the duration should to be limited to 14 days.

Fourteen trials were included with a total of 841 patients in systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis by Wittau et al. The authors have investigated that the use of antibiotic prophylaxis was not associated with a statistically significant reduction in mortality, in the incidence of infected pancreatic necrosis, in the incidence of non-pancreatic infections, and in surgical interventions (Wittau et al., 2011).

2.3 Epidural catheter

Severe acute pancreatitis is associated with the development of local complications, such as pancreatic and peripancreatic necrosis, abscesses or pseudocysts, and systemic complications, such as adult respiratory distress syndrome or renal failure with mortality rate is close to 15 % (Demirag et al., 2006). The pathophysiology of acute pancreatitis is incompletely understood but alteration in the pancreatic microcirculatory blood flow has been involved. Thus, a decrease in pancreatic blood flow occurs early in the course of acute pancreatitis and has been suggested to play a role in the conversion of edematous to necrotizing acute pancreatitis (Klar et al., 1994). The microcirculatory dysfunction includes arterial vasoconstriction with hypoperfusion, ischemia-reperfusion injury and obstruction of the venous outflow (Klar et al., 1991; Letko et al., 1994; Demirag et al., 2006).

Besides perfusion abnormalities, acute pancreatitis is also characterized by local and systemic inflammatory responses, including leukocyte activation as well as release of free radicals and cytokines (Frossard et al., 2001). Many therapeutic agents, such as dextran, heparin, procaine, L-arginine, antioxidants, or cytokine antagonists, have been tested experimentally and/or clinically to improve pancreatic tissue perfusion during acute pancreatitis, however, no significantly successful result has been achieved (Beger et al., 2001, Paszkowski et al., 2001). Epidural anesthesia that is used to induce analgesia in the

perioperative period might be an interesting treatment of the microcirculatory blood flow abnormalities (Demiraget al., 2006).

2.4 Type of surgical intervention

Severe acute pancreatitis is still related to high mortality rates. Over the past decades, management of severe acute pancreatitis changed from an early operative treatment to a more conservative approach. Surgical debridement is the gold standard in patients with infected pancreatic necrosis. However surgical intervention for sterile necrosis is only indicated in selected patients if aggressive intensive care is unsuccessful. Patients suspected to have infected pancreatic necrosis, should undergo computer tomography-guided or ultrasound-guided fine-needle aspiration for verification. By delaying surgery up to the third week, sufficient debridement can be achieved by a single operation, resulting in low mortality and morbidity rates.

2.4.1 Operative treatment of pancreatic necrosis

In patients with infected pancreatic necrosis, surgical necrosectomy is the established gold standard, whereas operative treatment of patients with sterile necroses is controversially discussed. Surgical debridement of infected pancreatic necrosis is based on two principles (Sahora et al., 2009). First, necrotic pancreatic tissue as well as pancreatic ascites is removed out of the peritoneal cavity and the lesser sac, to prevent absorption through the thoracic duct, which is accused to increase the incidence of systemic complications as development of single or multiple organ failure (Mayer et al., 1985). Second, as much as possible viable pancreatic tissue should be preserved to insure a good quality of life after recovery (Broome et al., 1996). Nowadays mortality in patients with infected pancreatic necrosis is about 10–30% in specialized centers as a result of right timing and patient selection (Büchler et al., 2000). Because of improvements in intensive care medicine, today more patients survive the first phase of acute pancreatitis, increasing the incidence of infected necrosis (Beger et al., 1986). Retroperitoneal gas or bacterial culture gained from fine-needle aspiration (ultrasound or computer tomography guided) is confirmation for infected pancreatic necrosis. Sterile necrosis, in general, is no indication for surgery. Multiple series have shown that patients with sterile necrosis can be managed by a conservative approach, but surgery might be indicated in case of late complications, disease progression or persistence. In these severely ill patients, who develop organ failure without signs of septic complications, the indication to surgery must be made individually (Sahora et al., 2009). As in patients with infected necrosis, early operation has shown high mortality rates and should also be delayed upon the third week (Büchler et al., 2000; Uhl et al., 2002; Hartwig et al., 2002a).

In the past, early surgical intervention was indicated for patients with severe acute pancreatitis, but was lead to mortality rates up to 65% (Smadja & Bismuth, 1986). The aim of this intervention was that patients would benefit from the initial removal of necrotic tissue, leading to the reduction of multisystemic complications related to enzymes and toxic substances (Fernandetz –Cruz et al., 1994). For evaluation of mortality rates, early surgical intervention was compared to a more conservative approach. In retrospective study performed by Hartwig et al., and in randomized control trial made by Mier et al., was found reduction of mortality rates in patients undergoing delayed surgery (Mier et al., 1997; Hartwig et al., 2002a).

At present, guidelines for the management of surgical treatment of severe acute pancreatitis agree that surgical intervention should be delayed as long as 3–4 weeks after onset (Uhl et al., 2002; Isaji et al., 2006). By deferring surgery a proper demarcation of pancreatic and peripancreatic necrosis can take place. The demarcation of necrotic masses from viable tissue enables an easier and safer debridement with a greater likelihood of sparing pancreatic tissue and leads to successful surgical control of pancreatic necrosis. Thus the risk of bleeding and the surgery-related loss of vital tissue that predisposes to surgery-induced endocrine and exocrine pancreatic insufficiency can be minimized by this approach (Hartwig et al., 2002b, Bober et al., 2003).

The aim of any intervention technique is to maximize debridement, preserve as much vital pancreatic parenchyma as possible and to secure postoperative drainage of debris and exudates (Götzinger et al., 2002). Resection procedures, as partial or total pancreatectomy, which also remove vital tissue, have been abandoned, because of impaired quality of life and higher mortality and morbidity (Nordback & Auvinen, 1985). Several open and minimal invasive techniques have been described, but an ideal method has not yet been defined. The surgical procedures including: open necrosectomy with closed continuous lavage, open necrosectomy with drainage and relaparotomy on demand, open necrosectomy with open packing and planned re-laparotomy. However morbidity (80%), including pancreatic, intestinal fistula, stomach outlet stenosis, local bleeding, and incisional hernia, is higher in patients undergoing multiple relaparotomies, which are mandatory in open packing procedure (Beger et al., 1982; Büchler et al., 2000; Fernandez-del Castilo et al.,1998).

The open approach for the surgical treatment of severe acute pancreatitis including blunt debridement is combined with laparostomy for drainage and access for revisions to further remove local debris. Operative access is gained by a way of a midline incision. Careful exploration is done to assess the extent of pancreatic and extrapancreatic necrosis, including a Kocher's mobilization of the second part of the duodenum. Furthermore the right and the left colon are mobilized. It is possible to approach the lesser sac through the gastrohepatic omentum or the gastrocolic omentum. If opening of the lesser sac is not possible because of a bounded inflammatory process, direct access from the infracolic compartment via the left transverse mesocolon is an alternative. The access through the mesocolon also allows drains to be placed in a more exact position once the debridement is completed. It is important to send fluid collection from the necrotic region for aerobic and anaerobic culture (Sahora, 2009). After sufficient debridement there remain cavities, which are often stiff and may bleed from the granulated surface. In these spaces is necessity to place 4–10 easy flow drains, which are brought out through left and or right side placed laparostomas. These drains are not removed unless the daily quantum of fluid loss is less than 20 ml. Another possibility is to stepwisely remove these drains that will result in a fistula due to a mature fistula tract. This fistula will close in a given period (Sahora et al. 2009).

Today several additional techniques to open surgical necrosectomy have been described. Percutaneous drainage, endoscopic techniques, and minimal invasive surgical procedures have been described as additive and alternative procedures. Percutaneous computer tomography-guided catheter debridement without surgery has been shown to be feasible in selected series in more than 50% of the included patients, with infected and sterile necrosis. Mortality rates of 12–30%, of patients treated by percutaneous drainage only, have been reported, using different access routes and a variety of catheter types (Bruennler et al., 2008;

Mortelé et al., 2009). The major reported complications were hemorrhage and injury to adjacent organs. The endoscopic drainage of sterile pancreatic necrosis using several transgastric and transduodenal catheters combined with a nasopancreatic catheter to lavage the necrotic cavity described Baron in 1996 (Baron et al., 1996). Using endoscopic drainage, many authors reported a high percentage of patients, who were treated without the need of surgery (Baron et al., 2002, Seifert et al., 2009, Seewald, 2005). Recently also minimally invasive necrosectomy techniques have been used with some promising results. Different approaches are described to access the necrotic mass. Some authors prefer a transabdominal access, which offers a good overview but harbors the risk of spreading intra-abdominal infection. As an alternative the necrotic focus can be reached through retroperitoneoscopy. Bücher et al. reported a group of 8 patients who underwent minimal invasive necrosectomy using a single large port, inserted over the percutaneous drainage channel. Complication rate was zero and despite one patient only a single session was needed (Bucher et al., 2008). Alternatively Parekh describes a laparoscopic hand-assisted method, using a transabdominal approach. In this series 19 patients, out of 23, were treated without the need of open laparotomy, zero postoperative complications, and a mortality of 10.5% (Perehk, 2006).

In conclusion, comparison of these minimal invasive procedures is almost impossible because of inhomogenity of patient selection. Today there are no randomized controlled trails comparing open surgery to one of the mentioned methods. Minimal invasive procedures may play a role in bridging the time to definite surgery in critically ill patients in some well-experienced clinical centers (Sahora et al., 2009).

2.4.2 Intra-abdominal hypertension

Intra-abdominal hypertension is increasingly reported in patients with severe acute pancreatitis, and is caused by several factors, including visceral edema and ascites associated with massive fluid resuscitation, paralytic ileus and retroperitoneal inflammation. There is a strong relation with early organ dysfunction and mortality in these patients, which makes intra-abdominal hypertension an attractive target for intervention. Several reports conclude that this phenomenon occurs within the first 5 days after admission, and that the kinetics of inta-abdominal hypertension is important: patients with persistent intra-abdominal hypertension seem to be at the highest risk for mortality. Several strategies to reduce intra-abdominal pressure have been developed, and given the pathophysiology, percutaneous drainage of ascites is a first logical step. However, if conservative measures fail to reduce intra-abdominal pressure in a setting with ongoing or worsening organ dysfunction, abdominal decompression is recommended. Intra-abdominal hypertension and intra-abdominal compartment syndrome have been described most often in patients with abdominal trauma or after emergency abdominal surgical procedures such as aortic aneurysm repair (De Waele, 2008). The intra-abdominal hypertension is defined as a sustained or repeated pathologic elevation of the intraabdominal pressure above 12mm Hg. The intra-abdominal compartment syndrome is described as the sustained elevation of intra-abdominal pressure above 20mmHg in combination with newly developed organ dysfunction (Malbrain et al., 2006).

It was shown that intra-abdominal hypertension is associated with higher mortality and morbidity rates, and prolonged intensive care unit stay, in comparison to other patients who had normal intra-abdominal pressure (Sugrue et al., 1999). Intra-abdominal hypertension has been recognized as a cause of organ dysfunction in critically ill patients, including those

suffering from severe acute pancreatitis (Balogh et al., 2002). Placement of a urinary catheter for the monitoring of intra-abdominal pressure would be necessary in the severe acute pancreatitis patients. The symptoms caused by intra-abdominal hypertension in patients with acute pancreatitis are not very different from other conditions associated with intra-abdominal hypertension. Hemodynamic instability requiring vasoactive drugs, acute renal failure and respiratory failure are the most obvious clinical signs and symptoms that have been associated with intra-abdominal hypertension. The association between intra-abdominal hypertension and development of organ dysfunction in severe acute pancreatitis is well documented. De Waele et al. showed that there was a 95% incidence of respiratory failure, 91% cardiovascular and 86% acute renal failure rate in patients with intra-abdominal pressure of 15 mmHg or higher (De Waelle et al., 2005). The development of intra-abdominal hypertension in patients with severe acute pancreatitis is evidently an important problem, as it is associated with organ dysfunction and mortality. Therefore, intra-abdominal pressure should be measured routinely in patients admitted to the intensive care unit with severe acute pancreatitis, and intra-abdominal pressure should be considered a target for intervention in all patients.

Decompressive laparotomy has been shown to effectively reduce intra-abdominal pressure and reverse the symptoms typically associated with abdominal compartment syndrome (De Waelle et al., 2006; Dambrauskas et al., 2009). If decompression is needed more than 2–3 weeks after the onset of the disease and there is evidence of extensive necrosis on a computered tomography scan or established infection of peripancreatic necrosis, it is the feasible to perform a necrosectomy in conjunction with the decompressive laparotomy. In selected patients with extensive retroperitoneal fluid collections, a lumbotomy may provide access to the retroperitoneal space, and allow evacuation of pancreatic necrosis as well. The management of the open abdomen following decompression in severe acute pancreatitis is challenging. The best currently available technique is the utilization of the vacuum-assisted closure technique aiming for gradual closure of the abdominal wall. The use of a vacuum assisted closure system guarantees a perfect seal of the peritoneal cavity, avoiding possible superinfection of the pancreatic or peripancreatic necrosis.

Intra-abdominal hypertension seems to have a significant role in contributing to the early multi organ dysfunction syndrome, subsequent complications and mortality in severe acute pancreatitis. Intra-abdominal pressure monitoring is mandatory for all patients who develop organ dysfunction, and intra-abdominal pressure should be a target for intervention when intra-abdominal hypertension and organ dysfunction persist. Surgical decompression should be considered in all patients with persistent organ dysfunction after 3 days or later (Sugrue et al., 2007; De Waele, 2008).

3. Clinical group of patients and the methods

All patients who were hospitalized due to the acute pancreatitis symptoms in the period from January 2003 till December 2008 at the First Department of Surgery, University Hospital, in Kosice, were included to this study. Those patients, who were primarily hospitalized and treated at other workplaces and were moved to our institute during their disease, were excluded from this study.

The total number of the patients with acute pancreatitis during onset symptoms was 258 ones. All patients were hospitalized at the Intensive Care Unit, they received the standard intensive care (palliation of pain, nasal gastric tube, central vein catheter, urinary bladder catheter, intensive monitoring of the basic vital functions, intensive rehydratation treatment,

giving the inhibitors of proton pump, low molecular weight heparin, giving the prophylactic antibiotic therapy). In the case of biliary acute pancreatitis, mainly joined with jaundice, cholangitis or ultrasound suspicion for the presence of the stones in common bile duct, the patients were underwent urgent endoscopic retrograde cholangio-pancreatography during the first 48 hours after onset acute pancreatitis. The distinguishing of the mild forms and severe forms of acute pancreatitis were carried out using Ranson criteria, APACHE score, the daily follow-up of level C-reactive protein and measurement of percentage of involvement of pancreatic tissue by computer tomography severity index (Balthazar computer tomography scoring system). The first computer tomography examination was carried out first time after 48 hours from the beginning of disease. The diagnosis of the infected necrosis we did according to the clinical finding, inflammatory markers (white blood cells, C-reactive protein, procalcitonin), and ultrasound and computer tomography finding (presence of gas bubbles).
Patients with multi organ failure were moved from the Intensive Care Unit to be hospitalized at the Department of Anesthesiology and Intensive Medicine of our institute.
The clinical group of hospitalized patients was divided into two subgroups. Group A included the patients hospitalized from January 2003 till December 2005. This group of patients was evaluated retrospectively. The second Group B included the patients hospitalized from January 2006 till December 2008. This group was studied prospectively, according to the clinical protocol prepared in advance, which reflected the changes in management of the patients with the severe acute pancreatitis after confirmation of necrosis.
Fisher's exact and Pearson chi-square tests were used in data analysis. $P < 0.05$ was considered statistically significant.

3.1 Clinical protocol of changes in management of treatment acute pancreatitis patients

Enteral nutrition fed by the three-luminal tube applied by fibroscope, checking the position by the contrast X-rays exam or by enteral nutrition through jejunostomy, in the case of already operated patients. Enteral nutrition was applied if no signs of the cardiovascular instability were present. We used the enteral nutrition enriched of the glutamine, arginine and omega-3 fatty acids and fibres. The dose was gradually increased from 20ml/hour to 80ml/hour (maximum 1000ml/24 hours). The enteral nutrition was started at seven o´clock in the morning and takes 12.5 hours to half past seven in the evening. At night, the enteral nutrition was not administrated. The second change includes an application of the epidural catheter to palliate the pain and to recovery of intestinal peristaltic. The continual measurement of the intra-abdominal pressure with the catheter in urinary bladder was used. The changes in the prophylactic application of antibiotics include changing III.generation cephalosporin's which were administered in Group A for imipenem which were replaces in Group B. In both groups the prophylactic application lasted maximum 14 days. Necrosectomy was indicated and performed as late as possible; usually the surgical procedure was pushed to the third or fourth week of hospitalization.

3.2 Results

Basic characteristic of both subgroup A and B are documented in table 1. It follows less frequency in Group A, however the male/female ratio and occurrence of the severe acute pancreatitis was similar. The percentage of the patients with necrotic pancreas and the

patients, who needed endoscopic retrograde cholangiography procedure, was similar as well.

	Group A	Group B
Number of patients	97	161
Male/Female	53 : 44	90 : 71
Mild acute pancreatitis	84 (86%)	132 (82%)
Severe acute pancreatitis	13 (14%)	29 (18%)
Number of patients + endoscopic retrograde cholangiopancreatography	34 (35%)	53 (33%)

Table 1. Groups of patients suffered from acute pancreatitis, group A (2003-2005), group B (2006-2008).

Further we will be concerned only with the patients with severe acute pancreatitis. More detailed characteristic of patients with severe acute pancreatitis is documented in table 2.

	Group A	Group B
Number of patients	13	29
Male/Female	8/5	16/13
Mean of age	38,5 year	42 year
Etiology of acute pancreatitis Alcohol Biliary disease Other	 7 (54%) 5 1	 14 (48%) 12 3
Ranson score	3,9 (3-9)	4,0 (2-9)
Number of patients with computer tomography scan necrosis more than 30%	12 (92%)	26 (90%)
Patients hospitalized at the Department of Anesthesiology et Intensive Medicine	6 (46%)	11 (37%)

Table 2. Group of patients suffered from severe acute pancreatitis

More detailed description of group of patients with severe acute pancreatitis is documented in table 2. In both groups of patients there is a dominance of male and the similar average age, Ranson score, as well as a number of patients with necrotic pancreas over than 30%. Alcoholic etiology occurred more often in Group A. Also we noticed the higher number of patients, who needed hospitalization at the Department of Anesthesiology and Intensive Medicine. During the hospitalization, mainly during the period from 72 hours to 7th day, we provided intensive treatment in both group of patients, however in some cases in spite of our intensive effort, the multi organ failure occurred. In the case of presence of abdominal compartment syndrome, we indicated the surgical intervention including intra abdominal decompression. Presence of the infected pancreatic necrosis or abscess was a clear indication for surgical intervention. Individual indications and the timing of the surgery are presented in table 3.

	Sterile necrosis + multi organ failure		Infected necrosis		Abscess		Together		Mortality	
Time	A	B	A	B	A	B	A	B	A	B
Till 72 hours	1	1					1	1	1	1
Till 7 days	3	2					3	2	3	1
After 7 days		1	1				1	1		
After 14 days			1	3			1	3	1	1
After 21 days			1	4		1	1	5		
Together	4	4	3	7		1	7	12	5 71%	3 25%

Table 3. Timing of surgery, surgical indication and mortality in group A and group B.

In Group A, it is shown more often indications to the surgical intervention in the first days and weeks of hospitalization period. Comparing Group B, mainly in the case of infected necrosis, the surgical operations were pushed to the third or fourth week. This was reflected also in the mortality of operated patients, when we recorded 71% mortality in Group A and 25% of mortality in Group B. The types of surgical procedures are documented in table 4. While during the first days we performed only the surgical revision and drainage, or open abdomen. In the case of infected necrosis we performed necrosectomy with closed continuous lavage. There are also documented the number of patients with reoperations in both groups of patients, which is less frequent in Group B.

	Primary surgery		Repeated surgery		Mortality	
Type of surgery	A	B	A	B	A	B
Revision, drainage, open abdomen, jejunostomy	2	1	0	0	2	0
Revision, drainage, jejunostomy	1	4	1	0	0	3
Necrosectomy, continuous lavage	4	7	2	4	3	0
Together	7	12	3 (43%)	4 (33%)	5	3

Table 4. Type of surgical procedures and mortality of patients in group of patients A and B.

The mortality in both groups of patients is presented in the Table 5. It shows less mortality in Group B (18%). Six patients were found with non infected necrosis 46% in Group A (2003-2005), but seventeen patients were documented with non infected necrosis 58% in Group B (2006-2008).

	Number of patients		Mortality	
	A	B	A	B
Acute pancreatitis patients	97	161	7 (7.2%)	5 (3.1%)
Severe acute pancreatitis patients	13	29	7 (53.8%)	5 (18%)
Severe acute pancreatitis patients after surgery	7	12	5	3
Severe acute pancreatitis patients with non infected necrosis	6	17	2	2

Table 5. Comparison of mortality of patients in group of patients A and B.

The comparison of the cause of the death in both groups is presented in table 6. There was statistically significant decrease in mortality in group of patients B (p=0.02).While only 2 patient's dead for the pancreatic sepsis with multi organ failure, the remainder 10 patient's dead for multi organ failure in first days after the admitting to hospital.

	Group of patients A (2003-2005)	Group of patients B (2006-2008)	P
Number of patients	13	29	-
Death	7 (54%)	5 (18%)	0.02
Multi organ failure	6 (85%)	4 (80%)	-
Pancreatic sepsis	1 (15%)	1 (20%)	-

Table 6. Cause of death in both groups of patients A and B.

4. Discussion

Despite of the lasting dissatisfaction with the mortality level of the patients with severe acute pancreatitis, nevertheless during last decades as a consequence of the positive shift in diagnostic methods and treatment of acute pancreatitis, we succeeded to decrease mortality of severe acute pancreatitis patients to 10%-20% (Del Campos et al., 1998). During the last 15 years a big step was done towards the understanding and development of acute pancreatitis and at the same time the great progress in the screening methods of pancreas (Uhl et al., 2002). In line with the other authors opinions (Bank et al., 2002), taking into account own experiences, we are convinced that the decrease of the mortality was causes by an early recognition of the severe acute severe and setting up the prompt and appropriate treatment, by the improvement of the nutritional support, early endoscopic retrograde cholangiopancreatography supplied to the accurately indicated patients, and using the effective antibiotic treatment.

The International Association of Pancreatology proposed for acute pancreatitis treatment eleven recommendations (Sarr, 2003; Uhl et al., 2002), which created the framework for contemporary management of acute pancreatitis. These recommendations are based on the

principles of evidence based medicine. However, in many points, there is need of further comparative studies was observed.

Positive trend of the decreasing mortality in the cases of severe acute pancreatitis was visible also at our workplace. These results have been already published previously (Bober et al., 1995; Bober et al., 2002; Bober et al., 2003). During the period from 2003 to 2005 the results overall got worse, when the mortality level of severe acute pancreatitis increased to 53.8%. After in-depth analysis of the causes of this negative result, the decision to change management of the patients with acute pancreatitis was made. The new protocol was designed, which contained the change of the management.

The contemporary standard of management of acute pancreatitis is the intensive conservative treatment with possibility of the diagnosis of its complications in the course of the therapy (Huťan, 2006). Very important part of the acute treatment is early and adequate fluid resuscitation during the first hour after admission in the case of patients with cardiovascular instability. When diagnosis of acute pancreatitis is confirmed, the treatment in line with a new protocol was applied.

Many reports were published about the positive influence of the early enteral nutrition in the case of severe acute pancreatitis. Cao et al. published the results of meta-analysis, which compared the results achieved by the enteral nutrition and total parenteral nutrition in the case of severe acute pancreatitis. Patients with enteral nutrition have shown less risk of infection, less percentage of pancreatic and peripancreatic necrosis, as well as, less overall complications, less often multi organ failure and low mortality (Petrov et al., 2006; Cao et al., 2008). Application of the three-luminal tube with help of fibroscope was carried out in our Group B by own co-workers, who had enough experiences and own endoscopy certificate. The application of the gastric aspirate and the enteral nutrition was tolerated well by all patients. Some of them perceived the abdominal discomfort and the slight increasing of the intra abdominal pressure. In these cases we have temporarily reduced the volume of the enteral nutrition.

The aim of the prophylactic application of antibiotics is to protect the sterile necrotic tissue against the development of infection. In general, it is accepted, that 40%-70% necrosis is infected. With regard to the high percentage of this infection of pancreatic necrosis and with regard to the fact that mortality is higher in the case of infected necrosis than in the case of sterile ones, the preventive application of antibiotics prevention, which has to avoid the infection of the necrosis. The reason is except an unproved benefit from prevention also its possible risks (antibiotic resistance and development of mycotic super infection from antibiotics) (Dambraukas et al., 2007; Dellinger et al., 2007; Olejník & Brychta, 2008). At present, the routine application of the prophylactic antibiotics to the patients with proven necrosis, has many supporters (Xu & Cai, 2008; Rokke et al., 2007; Dambraukas et al., 2007; Otto et al., 2006; Uhl et al., 2002). The conclusions of their studies show that antibiotics prevention reduces the sepsis and mortality. The recommendation in International Association of Pancreatology reports that prophylactic application of broad-spectrum antibiotics reduces infection of computer tomography confirmed necrotic acute pancreatitis, but it does not improve survival rate. When choosing the antibiotics, it is pointed at the best results Imipenem or Meropenem (decrease of necrosis, less necessities to surgical treatment, lower mortality) (Carter et al., 2000). Comparing Imipenem and Meropenem, no differences in incidence of the septic complications were observed (Heinrich et al., 2006). Preventive antibiotics have to be administered during 7-14 days. Longer applications than 14 days is

not recommended (Olejník & Brychta, 2008). Regarding the different opinions on the antibiotics prophylaxis, it is necessary to take into account the extent of necrosis of the pancreas. If the damage is less than 30% of pancreas parenchyma, the risk of infection is small (Olejník & Brychta, 2008). Despite of all contra version, many, also prestigious workplaces, at present administer the antibiotics prophylaxis in the case of severe acute pancreatitis, bearing the risk of contra productive effect. We assigned our workplace to this group.

In the cases of patients with severe acute pancreatitis, it is necessary from the beginning or during the treatment, in spite of the intensive conservative one, to consider the indication of the surgical treatment. During the initial phase after admission of patients with acute pancreatitis the situations appear, when in spite of the precise differential diagnostics (based on anamnesis, clinical examination, laboratory tests, ultrasound) these does not bring the clear breaking up and the indication of diagnostic exploration can be actual. Computer tomography examination can be very helpful in such situations and it can decrease these doubt to minimum. Despite of the risk of surgery, the published opinions say, that it is less probable, that the diagnostic exploration exacerbated local inflaming process, though it can increase the risk of infection of pancreatic necrosis. This risk should be reevaluated in situation, when there is no other alternative approach in treatment without surgical intervention (Dugernier et al., 2006).

The indications for surgery which are also now discussed are the patients with sterile pancreatic necrosis and multi organ failure, which are non-responsible to the intensive treatment more than 72 hours. In the literature, there is a published opinion, that patients with high extent of pancreatic necrosis with persistent multi organ failure, in spite of maximum intensive care, can have a benefit from surgery. The clinical status has to be revaluated daily, because the right timing of surgical intervention is very important. Intensive care is suitable until the indications for surgical solution are not fulfilled (Götzinger et al., 2002).

In our group of patients we indicated the surgical treatment for 7 patients in 7 days after admission to hospital. In this group of patients, we recorded 86% mortality (in Group A 100%, in Group B 67%). Some authors recommend surgical intervention to the patients with sterile necrosis, whose status is not improved during four weeks of intensive care (Hartwig et al., 2002b).

A right timing of necrosectomy is discussed up till now. Those, who propose an early surgery say, that patient benefits from the early removal of the tissue necrosis, as it results to the decreasing of the multisystem complications linked with the releasing of enzymes and toxic substations. In the past, an early surgical intervention was preferred especially in the cases of system functions damage, but it resulted to the high mortality (Götzinger, 2007).

Götzinger study pointed at the fact that a benefit from the delay of the surgical intervention is in the enclosure of demarcation process of dead tissue. This demarcation enables the safe and sufficient following debridement, which leads to be successful surgical control of pancreatic necrosis in one or more steps. The analysis of the timing showed, that necrosectomy performed after three weeks from the beginning of illness is linked with higher percentage of success of debridement of pancreatic necrosis, what results to the lower number of reoperation and lower mortality. Very early debridement (up to three weeks) means an oversize percentage of mortality (Götzinger, 2007).

In rare situation, also intra-abdominal hypertension is an indication to decompressive laparotomy (Šiller et al., 2007). Intra-abdominal hypertension is caused by paralytic ileus, by large inflammation of retroperitoneal tissue, increased vascular permeability and also by liquid collections in abdominal cavity. It can be caused also by aggressive liquid hyper resuscitation (Dugernier et al., 2006).
Intra-abdominal hypertension is typical at the beginning of illness and can lead to the intra-abdominal compartment syndrome (the intra-abdominal pressure is higher than 20mmHg), which can make worth organ dysfunctions (Malbrain et al., 2006).
At present some indications to surgical treatment are apparent and clear. The absolute indications to the urgent surgery are necrosis and pancreatic or peripancreatic abscess. Infected necrosis begins at 40-50% patients with necrotic acute pancreatitis (Hartwig et al., 2002b). Infected necrosis means the necrotic area with bacterial contamination in devitalized tissue. Necrosis of pancreas and peripancreatic tissue is the risky environment for bacterial contamination. The risk of pancreatic infection grows with the volume of devitalized tissue. It culminated in the third week from the beginning of the illness. But 25% of patients have the infection during first 7 days (Dugernier et al., 2006).
Although acute pancreatitis is at the beginning a sterile inflammatory disease, which leads to multi organ dysfunctional syndrome, so the clinical features are difficult to distinguish from severe sepsis. The confirmation of presence of infection is when gas bubbles are found on the computer tomography examination, also by the positive cultivation of specimen obtained from the necrosis by thin-needle technique. This technique is safe and 90% precise (Schmid et al., 1999).
Bacterial translocation from intestinal lumen (transmurally, by lymphatic and vascular way, by ascites) is the main mechanism of the infection transfer to the necrosis during the first weeks of the disease. The microbiological examination shows that the origin of infection of pancreas is first of all the intestinal infections. Later sources are nosocomial infections of staphylococcus and enterococcus, including the multiresistant microorganism and mycotic infections (Büchler et al., 2000). At present, the accepted opinion is that necrosectomy has to be done as soon as the evidence of the infected necrosis is confirmed (Huťan, 2008).
The approach of the surgical treatment of necrotic acute pancreatitis has been developed. Some of them are obsolete (resection methods), but various techniques of the necrosectomy of pancreatic and peripancreatic necrosis remain as dominant approach done by the classic open surgery, by laparoscopic retroperitoneal miniinvasive surgery or percutaneous necrosectomy.
Additional techniques (after necrosectomy) are based on knowledge, that during surgical intervention it is not possible to remove all necrosis, because demarcation is not complete and too radical removal of this necrosis causes rather damage than benefit. On the other hand the rest of the necrosis can be a source of the persistent sepsis.
From the range of additional techniques may be mentioned the conventional surgical drainage with closing of the abdominal cavity and with location of the gravity or suck tube drains, open abdomen techniques also called laparostomy and at last the closed continuous lavage. It is possible to combine to abovementioned additional techniques.
Own experiences with all additional technique have been published already (Bober et al., 2003). At present we use all of them, but we prefer the closed continuous lavage technique of bursa omentalis and retroperitoneum, as we published in 2003, accepting also results of comparative studies (Beger et al., 2002; Branum et al., 1998).

Delay of the necrosectomy to the third –fourth week of hospitalization with applying the closed continuous lavage we obtained very good results in number of postoperative local complications as well as in the need of reoperations and no mortality in this subgroup of patients.

During last year's many works were published about retroperitoneal necrosectomy (Connor et al., 2005; Van Santvoot et al., 2007) laparoscopic assisted percutaneous drainage of infected necrosis and peripancreatic abscess (Horvath et al., 2001), laparoscopic necrosectomy (Cushieri et al., 2002; Risse et al., 2004; Šutiak et al.,2008). Also other authors published the report about very positive results with percutaneous necrosectomy (Bruennler et al., 2008; Hartwig et al., 2002a). The benefit of percutaneous necrosectomy is mini invasive approach, which does not require total anesthesia, but the disadvantages are: longer time of hospitalization, higher doses of X-ray because of repetitive computer tomography controls and high percentage of cases, when patients had to perform of laparotomy due to the insufficiency of previous one.

Pancreatic abscess contrary to the infected necrosis is well demarcated collection of purulent liquid without solid necrotic material. It is a result of infection, which arises from accumulation of liquid collections or from the area of necrosis, which has liquidized in the meantime. Comparing with the infected necrosis, the pancreatic abscess appears later (more than four weeks from the beginning of a disease) and the prolonged process is typical for it (Fernandez Del Castilo et al., 1998). If the pancreatic abscess contains small, solids particles, very often it is not suitable to drain it in percutaneous or endoscopic way (Baril et al., 2000; Carter et al., 2000).

The other indication for surgery is the course of severe acute pancreatitis is bleeding. The intensive inflammation, large regional necrosis and secondary infection cause arouses of great vessels and cause a pseudoaneurysm, which rupture may cause massive hemorrhage to gastrointestinal tract, retroperitoneum or abdominal cavity.

The early diagnosis and following intervention radiology and surgical treatment are necessary for bleeding control. Debridement of the infected necrosis is the effective management for minimizing the risk of recurrent bleeding. Fortunately, the incidence of the hemorrhagic complications of severe acute pancreatitis decreases due to early recognition and intensive treatment of these patients (Huťan, 2008).

5. Conclusion

Despite the mortality of severe acute pancreatitis decreased after the implementation of new diagnostic and medical procedures in last two decade, many questions are still open. Recent studies of severe acute pancreatitis were reviewed and the decision to change the management of the treatment of severe acute pancreatitis has been made. The management referred to the enteral nutrition, epidural analgesia, antibiotic prophylaxis, delay surgery to the later period (three-four weeks after onset) in the case of infected necrosis.

Using enteral nutrition in preventing septic complications of acute pancreatitis seems to be better than parenteral nutrition. Epidural anesthesia is used to induce analgesia, to recovery of intestinal peristaltic and for improvement of the microcirculation blood flow. The continual measurement of the intra-abdominal pressure with the catheter in urinary bladder was used. After confirmation of necrosis, the prophylactic application of antibiotics including imipenem was used for severe acute pancreatitis patients. The prophylactic

application lasted maximum 14 days. By deferring surgery a proper demarcation of pancreatic and peripancreatic necrosis can take place. The demarcation of necrotic masses from viable tissue enables as easier and safer debridement with a great likelihood of sparing pancreatic tissue and leads to successful surgical control of pancreatic necrosis.
Applying the change of the management of treatment of the patients with the complicated form of acute pancreatitis, there were found an interesting results, which could recommended to use this management for patients suffered from severe acute pancreatitis.

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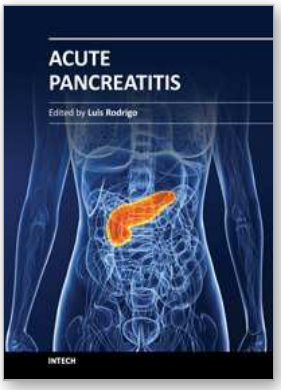

Acute Pancreatitis

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Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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