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Original article

Analysis of Treatment-Related Factors Affecting Mortality in Patients with Severe Necrotizing Acute Pancreatitis

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SUMMARY

The aim of the paper was to determine the factors related to the initial therapy that may contribute to death from severe necrotizing acute pancreatitis and to analyze their clinical importance as well as possible additive effects.

A retrospective case-control study included all adult patients treated for severe necrotizing acute pancreatitis in the Clinical Center of Kragujevac, Serbia, during the five-year period (2006-2010.). The cases (n = 41) were patients who died, while the controls (n = 69) were participants who survived. In order to estimate the relationship between potential risk factors and observed outcome, crude and adjusted odds ratios (OR) with 95 % confidence intervals (CI) were calculated in logistic regression models.

Significant association with observed outcome was shown for the use of gelatin and/or hydroxyethyl starch (adjusted OR 12.555; 95 % CI 1.150-137.005), use of albumin (adjusted OR 27.973; 95 % CI 1.741-449.373), use of octreotide (adjusted OR 16.069; 95 % CI 1.072-240.821) and avoiding of enteral feeding (adjusted OR 3.933; 95 % CI 1.118-13.829), while the use of nonsteroidal anti-inflammatory drugs had protective role (adjusted OR 0.057; 95 % CI 0.004-0.805).

The risk of death in patients with predicted severe necrotizing acute pancreatitis could be reduced with avoidance of treatment with colloid solutions, albumin and octreotide, as well as with an early introduction of oral/enteral nutrition and use of nonsteroidal anti-inflammatory drugs.

Key words: **pancreatitis, acute necrotizing, risk factors, death, albumin**

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INTRODUCTION

Severe necrotizing acute pancreatitis is a multisystem disorder, characterized by pancreatic and/or peripancreatic tissue necrosis and widespread inflammatory response leading to single or multiple organ dysfunction which does not resolve within the first 48 hours (the so-called persistent organ failure according to revised Atlanta criteria 2012) (1). It occurs in about 15-20 % of all cases of acute pancreatitis (AP) and is considered the most serious disease course due to high complications and death rates despite recent diagnostic and therapeutic advancements; the mortality may be particularly high if necrotic areas become infected, exceeding 50 % when infection and persistent organ failure develop during the first week of the illness (1-4).

In the light of these facts, taking also into account variable and unpredictable course of AP, current recommendations emphasize appropriate early management based on careful initial risk assessment in all patients presenting with AP on admission to hospital (1, 4). Dealing with this issue, previous studies have identified numerous factors that are only associated with or may contribute to the development of severe disease and increased mortality rate in patients with AP. Many of them are well-documented, such as older age, obesity, idiopathic AP, important comorbidities, as well as certain clinical, laboratory and radiologic parameters of disease severity on initial evaluation (signs of systemic inflammatory response syndrome, hypotension, altered mental status, high packed cell volume, elevated creatinine and blood urea nitrogen, increased fasting blood glucose, high level of C-reactive protein, pleural effusion and/or pulmonary infiltrates, and others), while the factors relating to various treatment options (including medication choice and dose regimens) are still not clearly defined (1). As a matter of fact, the only measures that have shown unequivocal effectiveness in reducing the risk of complications and death in patients with severe AP were early aggressive fluid replacement and early enteral nutritional support (1, 4). On the other hand, roles of antibiotic prophylaxis and of other medication remain controversial in terms of possible beneficial or detrimental effects (1, 4). In addition, mutual interactions of risk factors for death of severe AP were not investigated extensively, except for organ failure and infection of pancreatic necrosis (3).

The aim of this study was to determine potentially modifiable factors that can influence mortality of patients with severe necrotizing AP (with specific focus on certain components and modalities of initial conservative treatment), and to analyze their clinical relevance as well as possible synergistic effects in a clinically meaningful manner.

MATERIALS AND METHODS

Study settings

The present study was carried out at the Clinical Center of Kragujevac, Serbia, an institution providing tertiary healthcare services to approximately two million inhabitants of Central and Western Serbia. The study population included all patients treated for acute pancreatitis in Surgical Intensive Care Unit (SICU) of the Clinical Center of Kragujevac (CCK) who had been classified to have severe disease according to the original Atlanta criteria from 1992 (5) with pancreatic necrosis confirmed by adequate imaging, during the five-year period, between January 1, 2006, and January 1, 2011. All necessary data on demographic and clinical characteristics of the patients, diagnostic tests results, and on treatments and outcomes, were obtained from the patients' files. The approval of this study was obtained from the Ethics Committee of CCK before the first patient was enrolled.

Study design

This study was retrospective and observational, and the case-control design was chosen. The patients with severe necrotizing pancreatitis (n = 110) were divided into two groups with respect to the main study outcome: the group of patients who died (cases, n = 41) and the group of patients who survived (controls, n = 69). Based on retrospective review of the patients' files, these two groups were compared in terms of differences in exposure to the observed risk factors.

The following patients were excluded from the study: those under 18 years of age, those with acute postoperative pancreatitis, pregnant women with acute pancreatitis, patients transferred from other hospitals or other wards to SICU of the Clinical Center of Kragujevac after more than 48 hours from the disease onset, as well as patients with incomplete medical records.

Study population

Along with the diagnosis of necrotizing AP verified by the findings of non-enhancement in pancreatic parenchyma after contrast administration exceeding 3 cm in size or 30 % of total gland area and/or by the heterogeneous fluid collection within the peripancreatic space containing solid material on abdominal computerized tomography (CT) scan, all included patients also met Atlanta 1992 criterion of disease severity referring to the development of organ failure (hypovolemic shock or respiratory or renal insufficiency, i.e. systolic blood pressure <90 mmHg or PaO2 <8 kPa or blood creatinine level >177 μmol/ml (2 mg/dl) after fluid replacement) during the first week of the disease. For the purpose of detection of (peri)pancreatic necrosis, a single highly experienced radiologist had retrospectively evaluated and interpreted CT scans in a blinded manner with respect to the disease outcome, taking into consideration CT examinations that had been performed after at least three days from admission to SICU. In order to define severe disease course in this study, the original 1992 Atlanta classification of AP was used since the observation covered a period before the revision of these criteria in 2012. An additional reason is that persistent organ failure, as the major indicator of disease severity according to revisited Atlanta criteria (2), could not be properly evaluated in all patients due to the lack of relevant data in their files.

Potential risk factors

In the present study, the following categorical variables related to the initial treatment in SICU were analyzed as potential predictors of death of patients with severe necrotizing AP:

a) Type of intravenous solution used for fluid resuscitation; it was set as a dichotomous variable: only crystalloids vs. crystalloids plus colloids (gelatin and/or hydroxyethyl starch).

b) Use of albumin 20% solution (albumin was separated from other colloids since it is not routinely used for fluid replacement therapy, while on the other hand there are published data indicating deleterious effects of its use in critically ill patients in intensive care units); it was also set as a dichotomous variable.

c) Type of nutritional support starting within the first week of admission to SICU; this variable was divided into six categories:

1.No need for the nutrition support because regular oral feeding was resumed.

2.Total enteral nutrition via a nasojejunal tube.

3.Total enteral nutrition via a nasogastric tube.

4.Combined enteral and parenteral nutrition,

5.Total parenteral nutrition, and

6.Without any nutritional support, while regular oral feeding was not resumed.

d) Type of antibiotic used for the prevention of infection of pancreatic necrosis (the prophylactic use was defined as administration of an antibiotic immediately upon the admission to hospital); this variable had three categories:

1.Prophylaxis was not given

2.Use of carbapenems,

3.Use of 3rd generation cephalosporins or fluoroquinolones plus metronidazole

e)Use of nonsteroidal anti-inflammatory drugs (NSAIDs) set as a dichotomous variable (since only parenteral diclofenac 75 mg and/or ketorolac 30 mg were used in all patients treated with NSAIDs)

f)Use of opioid analgesics - set as a dichotomous variable (the tramadol was the only drug from this group used in the study).

g) Use of somatostatin analogue octreotide - set as a dichotomous variable (noting that somatostatin was not available for routine use in the Clinical Center of Kragujevac during the whole study period).

The relationship between the aforementioned therapy-related risk factors and observed outcome was adjusted for the influence of confounding variables such as patients' age and sex, and the total Multiple Organ Disfunction Score (Marshall MOD score, ranging from 0 to 24) (6) in the first 24 hours of admission to SICU as a reliable predictor of hospital mortality in seriously ill patients.

Data analysis

All observed characteristics were summarized using means and standard deviations for continuous variables or using frequencies and percentages for categorical data. The differences between compared groups in the means of continuous variables were analyzed by an independent Student's t-test or a tri-Mann-Whitney U test (depending on actual data disbution assessed by Kolmogorov-Smirnov test for normality), while categorical variables were compared using Chi-Square test for frequencies. In all analyses, the level of statistical significance was set at

alpha value of 0.05.

With the aim of determining predictors of death of severe necrotizing AP as well as their mutual interactions, crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were estimated using unconditional binary logistic regression analysis; clinically significant relationship was considered if OR was greater than 3 and its 95% CI did not include value of 1.

RESULTS

From the pool of 175 patients treated for severe acute pancreatitis in SICU of the Clinical Center of Kragujevac during the observational period, 110 (about 63%) fulfilled enrollment criteria for the study. Forty-one patient (37%) died from multiple organ dysfunction due to severe necrotizing AP, and 19 (54%) of them died within the first two weeks of admission to SICU. Based on the clinical, laboratory and in some cases also radiological findings (presence of gas bubbles on CT images), development of infected necrosis was suspected in 59% (24 / 41) of patients who died and in 22% (15 / 69) of survivors, which was a highly significant difference (Pearson Chi-square = 15.217, df =1, p <0.001). In addition, surgical treatment was used in 41% (17/41) of patients who died subsequently and in only four patients of 69 (6%) who survived; in the deceased group, significantly more patients underwent an operation within the first two weeks of admission to SICU (71%. vs. 29%), while among survivors the operations were undertaken only after this period (Pearson Chi-square = 15.217, df =1, p < 0.001).

Baseline characteristics of the deceased and surviving patients and differences between the groups in the exposure to potential risk factors for death from severe necrotizing AP are shown in Table 1. The greatest differences (p < 0.001) between the groups were observed for the total MOD score, type of solutions used in fluid replacement, use of albumins, and use of tramadol. With respect to the initial use of albumin, it is important to emphasize that an average serum albumin level on admission to SICU in patients of both groups who were subsequently treated with albumin 20% solution reflected the presence of mild to moderate hypo-albuminemia (27.75 ± 7.62 g/l, mean ± SD), and at the same time there was no significant difference between the compared groups in the serum albumin concentrations: 28.10 ± 7.72 g/l (mean ± SD) in a group of deceased patients vs. 29.60 ± 7.75 g/l (mean ± SD) in a group of survivors (t = 0.886, p = 0.378).

The results of both univariate and multivariate logistic regression analysis (Cox & Snell R square 0.643, Nagelkerke R square 0.878, Hosmer-Lemeshow Chi square 2.260, df = 8, p = 0.972, the overall model accuracy of 92 %) presented in Table 2 suggest that female sex, higher MOD score within the first 24 hours of admission to SICU, use of colloid solutions in fluid resuscitation, use of albumin 20% solution, use of octreotide and avoiding oral/enteral feeding (i.e. the use of total parenteral nutrition or non-use of nutritional support) are significantly associated with the occurrence of death due to severe necrotizing AP. Although the ORs for older age and use of opioid analgesic tramadol in univariate regression models indicated significant influence on the observed outcome (see crude ORs in the Table 2), after adjustment these effects were lost. On the other hand, use of NSAID may had a protective role reducing the odds of death for slightly more than 40%.

The mutual interactions between factors that are expected to have additive effects on the risk of fatal outcome in patients with severe necrotizing AP were also examined by the logistic regression model. The analysis (Cox & Snell R square 0.539, Nagelkerke R square 0.736, Hosmer-Lemeshow Chi square 2.226, df = 7, p = 0.946, overall model accuracy of 89%) showed clear and strong synergistic effects only for higher MOD score within the first 24h of admission to SICU and use of colloids for the fluid replacement and use of 20% albumin, while for female sex and older age as well as for avoidance of oral/enteral feeding and use of octreotide significant synergism was evident but it did not yield the level of clinical significance, i.e. adjusted ORs were slightly greater than 1 (Table 3).

DISCUSSION

The revised Atlanta Classification of acute pancreatitis emphasizes dynamic course of acute pancreatitis and its variable severity, which may lead to systemic complications with high mortality rate (2). High mortality rate from acute pancreatitis could be expected in the first two weeks of clinical course and as well as in the later phases of this disease (7). Severe systemic inflammatory response is mostly responsible for high mortality rate in early phase of acute pancreatitis, while pancreatic necrosis with consequent sepsis and multi-organ dysfunction syndrome are the main causes of death due to

Table 1. **Baseline characteristics of the study patients**

Variable	Deceased patients (cases) (n=41)	Surviving patients (controls) (n=69)	Test value and significance of null hypothesis	Crude odds ratios with confidence intervals (1.96*SE)
Sex (Male/Female)	M: 27 (66%) F: 14 (34%)	M: 52 (75%) F: 17 (25%)	$\chi^2 = 1,149$ $p = 0.284$	1.586 (0.680, 3.698)
Age (*years, mean ± SD*)	63.17 ± 14.78	56.16 ± 13.98	T = -2.490 $p = 0.014^{*}$	1.035 (1.006, 1.065)
Multiple Organ Dysfunction Score in the first 24 hours of admission to SICU (*mean ± SD*)	3.68 ± 2.46	0.85 ± 1.01	U = 256.00 Z = -7.200 $p< 0.001^{**}$	4.213 (2.462, 7.209)
Type of antibiotic (AB) used prophylactically	*without AB prophylaxis* 3 (7%) *carbapenems* 24 (59%) *other classes*§ 14 (34%)	*without AB prophylaxis* 2 (3%) *carbapenems* 52 (75%) *other classes*§ 15 (22%)	$\chi^2 = 3.660$ $p = 0.160$	1.357 (0.636, 2.896)
Use of nonsteroidal anti-inflammatory drugs	No: 23 (56) Yes: 18 (44)	No: 31 (44) Yes: 38 (56)	$\chi^2 = 1,284$ $p = 0.257$	0.638 (0.293, 1.390)
Type of solution used for intravenous fluid replacement	*only crystalloids* 5 (12%) *crystalloids plus colloids (gelatin and/or hydroxyethyl starch)* 36 (88%)	*only crystalloids* 50 (73%) *crystalloids plus colloids (gelatin and/or hydroxyethyl starch)* 19 (28%)	$\chi^2 = 37.367$ $p<0.001^{*}$	18.947 (6.472, 55.474)
Use of albumin 20%	Yes: 28 (68%) No: 13 (32%)	Yes: 6 (9%) No: 63 (91%)	$\chi^2 = 42,774$ $p< 0.001^{**}$	22.615 (7.797, 65.594)
Use of opioid analgesic tramadol	Yes: 29 (71%) No: 12 (29%)	Yes: 24 (35%) No: 45 (65%)	$\chi^2 = 13.312$ $p< 0.001^{*}$	4.531 (1.965, 10.449)
Use of octreotide	Yes: 24 (59%) No: 17 (42%)	Yes: 33 (48%) No: 36 (52%)	$\chi^2 = 1.182$ $p = 0.277$	1.540 (0.706, 3.361)

Nutrition support started within the first week after the admission to hospital	*not required (regular oral food intake restored)* 3 (7%) *total enteral nutrition through nasojejunal tube* 0 (0%) *total enteral nutrition through nasogastric tube* 2 (5%) *combined enteral and parenteral nutrition* 14 (34%) *total parenteral nutrition* 17 (415%) *without nutritional support* 5 (12.9%)	*not required (regular oral food intake restored)* 18 (26%) *total enteral nutrition through nasojejunal tube* 3 (4%) *total enteral nutrition through nasogastric tube* 0 (0%) *combined enteral and parenteral nutrition* 25 (36%) *total parenteral nutrition* 20 (29.0%) *without nutritional support* 3 (4.3%)	$\chi^2 = 13.294$ $p = 0.021^*$	1.523 (1.126, 2.060)© 0.143 (0.025, 0.807)£

SICU – surgical intensive care unit
χ^2 – Chi-square test
T – independent samples t-test, U – Mann-Whitney test
* - significant difference
** - highly significant difference
§- 3rd generation cephalosporins plus metronidazole or fluoroquinolones plus metronidazole
© - total parenteral nutrition and no nutritional support in the absence of restoring regular oral food intake were categories given the highest numerical code in the analysis
£ - oral/enteral feeding vs. total parenteral nutrition and no nutritional support

acute pancreatitis in its late phase (7). Modifying factors which can predict mortality in patients with severe acute pancreatitis are crucial in the management of this disease, since their change may improve the outcomes and reduce the total costs of severe necrotizing acute pancreatitis (8).

Protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) against the death outcome that was observed in our study is in accordance with recent reports on effectiveness of these drugs in prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) (9-11). It has been also observed in animal studies of acute pancreatitis that cyclooxygenase (COX) enzyme, especially isoform COX – 2 plays a significant role in early phase of inflammation in acute pancreatitis (12, 13). Phospholipase A2, the enzyme, which produces substrate for COX, is also elevated in serum of patients with acute pancreatitis, and may contribute to the development of acute and chronic complications of this disease (14, 15) through production of prostaglandins. NSAIDs inhibit the activity of both COX and PLA2, reducing their catalytic activity and decreasing production of proinflammatory prostaglandins; this effect may prevent the development of severe form of acute pancreatitis (16, 17).

Although theoretically opioids may increase the tone of Oddi's sphincter and therefore aggravate the course of acute pancratitis, this was not confirmed in the majority of clinical trials. On the contrary, recent studies have shown that pain in patients with severe pancreatitis was successfully treated with opioids or the combination of NSAIL and opioids, without increased risk of complications or death (18).The use of opioids in patients with severe pancreatitis decreases the need for additional analgesia. Recent clinical trials have shown that the use of opioids in patients with acute pancreatitis

Table 2. **Crude and adjusted odds ratios of the investigated factors potentially associated with death in patients with severe acute necrotizing pancreatitis**

Risk factors	Crude OR (95% CI)	Adjusted OR (95%CI)
Sex (female vs. male)	1.586 (0.680, 3.698)	20.554 (1.196, 353.361)**
Age	1.035 (1.006, 1.065)*	1.055 (0.980, 1.136)
Multiple organ dysfunction score in the first 24 hours after admission to SICU	4.213 (2.462, 7.209)*	8.394 (2.204, 31.973)**
Type of antibiotic (AB) used prophylactically	1.357 (0.636, 2,896)	1.405 (0.169, 11.708)
Use of non-steroidal anti-inflammatory drugs	0.638 (0.293, 1.390)	0.057 (0.004, 0.805)**
Type of solution used for intravenous fluid replacement (crystalloids plus colloids vs. crystalloids only)	18.947 (6.472, 55.474)**	12.555 (1.150, 137.005)**
Use of 20% albumin	22.615 (7.797, 65.594)**	27.973 (1.741, 449.373)**
Use of opioid analgesics (tramadol vs. no opioid analgesic was performed)	4.531 (1.965, 10.449)**	1.132 (0.166, 7.703)
Use of somatostatin/octreotide	1.540 (0.706, 3.361)	16.069 (1.072, 240.821)**
Nutritional support©	1.523 (1.126, 2.060)*	3.933 (1.118, 13.829)**

* only statistically significant association (OR)

** statistically and clinically significant association (OR)

© - total parenteral nutrition and no nutritional support in the absence of restoring regular oral food intake were categories given the highest numerical code in the analysis

does not increase the risk of complications of pancreatitis, and is without significant adverse reactions (19). Our study confirmed the results of these clinical trials, since administration of opioids to our patients did not increase their chances to die.

The Multiple Organ Dysfunction Score is a reliable instrument for measuring the level of organ dysfunction, risk of death and severity of various illnesses in intensive care units (20). Our results have shown that higher MOD score within the first 24 hours of admission was significantly associated with the occurrence of death due to severe necrotizing AP. This is not surprising, since severe forms of acute pancreatitis involve early onset of serious complications and systemic inflammatory syndrome that increase the MOD score (21). The MOD Score is an extremely useful clinical tool for risk stratification of patients with acute pancreatitis, which helps to physicians with deciding to undertake timely and adequate treatment, which may save lives of the patients.

The results of recent clinical trials stressed the positive role of nutritive support in recovery of patients with acute pancreatitis (22). Our study showed that witholding oral/enteral feeding when indicated increases the chances of a patient with severe necrotizing AP to die. Adequate nutritional status is a crucial segment of supportive care in patients with severe acute pancreatitis (20). Parenteral nutrition can lead to atrophy of intestinal mucosa and disruption of intestinal barrier in patient with severe acute pancreatitis (23). Advantages of early introduction of enteral nutrition in patients with severe acute pancreatitis are numerous. Enteral nutrition stimulates production of antiinflammatory cytokines in intestinal mucosa, increase motility of gastrointestinal tract and inhibit opportunistic pathogens (23). It was recently reported that enteral nutrition provides better regulation of glucose level in patient with severe acute pancreatitis (24). Hyperglycemia in patients with severe acute pancreatitis isrelated to increased production of oxidative stress elements and cytokines. Hyperglycemia in patients with acute pancreatitis enhances the risk of infections and increase mortality rate (24, 25). The enteral route of feeding maintain an adequate level of glucose in blood in patients with acute pancreatitis which gives them better chances for survival.

Table 3. **Interactions between the factors influencing mortality of patients with severe acute necrotizing pancreatitis**

Risk factors	Crude OR (95% CI)	Adjusted OR (95% CI)
Only sex (female vs. male)	1.586 (0.680, 3.698)	20.554 (1.196, 353.361)
Only age	1.035 (1.006, 1.065)	1.055 (0.980, 1.136)
Both sex and age	1.009 (0.997, 1.022)	1.022 (1.002, 1.042)*
Only Multiple Organ Dysfunction Score within the first 24 h of admission to SICU	4.213 (2.462, 7.209)	8.394 (2.204, 31.973)
Only type of solution used for the intravenous fluid replacement	18.947 (6.472, 55.474)	12.555 (1.150, 137.005)
Only use of albumin	22.615 (7.797, 65.594)	27.973 (1.741, 449.373)
Jointly Multiple Organ Dysfunction Score within the first 24 h of admission to SICU and type of solution used for the intravenous fluid replacement and use of albumin	4.213 (2.462, 7.209)	11.778 (3.057, 45.382)**
Only use of octreotide	1.540 (0.706, 3.361)	16.069 (1.072, 240.821)
Only nutritional support	1.523 (1.126, 2.060)	3.933 (1.118, 13.829)
Both use of octreotide and nutritional support	1.332 (1.059, 1.676)	1.713 (1.120, 2.619)*

* only statistically significant interaction

** statistically and clinically significant interaction

Somatostatin is a peptide hormone that regulates the endocrine system and has an inhibitory effect on production of pancreatic enzymes, which his the main mechanism for the treatment of AP. The influence of somatostatin or his analogue octreotide on mortality rate of severe AP was poorly described in literature, with controversial results. One study showed that administration of somatostatin to patients with severe AP can modulate immune inflammatory response and severity of AP, but difference in mortality between groups of patients with and without somatostatin was not observed (26). Another study suggested that somatostatin is effective, and recommended it for the treatment of acute pancreatitis (27). On the other side, there are studies that suggest that octreotide have no importance in the treatment of severe AP (28, 29). In our study, patients who received somatostatin or octreotide had more chances to die. Although we cannot explain this deleterious effect of somatostatin, we suggest cautious administration of this drug to patients with severe AP; Further studies are necessary to establish true effects of somatostatin on acute pancreatitis.

Intravenous fluid therapy is an important element of treatment of severe AP. Needs for fluids in severe AP are increased because of fluid sequestration and low peripheral tone of blood vessels. Some studies showed that proper choice of intravenous fluid can decrease morbidity and mortality in this patients (30, 31). Crystalloids are recommended fluids for therapy in patients with severe form of AP in the first place (32). According to the literature, the patients who were treated with cristalloides (normal saline 0.9%) or with a combination of cristalloides and colloides (hydroxyethyl starch - HES) had the same death rate (33). Recent studies showed that the use of HES in ICU in critically ill patients led to increased rate of renal-replacement therapy, but at the same time, there was no significant difference in mortality between patients who received 6% HES or saline (34). Our patients were infused with normal saline (0.9%), Ringer lactate, and 5 % glucose as cristalloids, what are the current recommendations, but also with a combination of cristalloids and colloids (gelatine and/or hydroxyethyl starch). According to our results, mortality rate was higher in patients who were treated with the combination of cristalloids and colloids, which is opposite to results of some other studies. While one study showed that the patients who did not receive aggressive intravenous fluid therapy in the first 24 hours had greater mortality rate (35), another did not prove that aggressive fluid therapy improve the outcome of patients with AP (36); however, in some cases pancreatic necrosis was prevented by aggressive fluid resuscitation which probably led to decrease mortality in patients with severe AP (30).

Albumin was administered to our patients in order to replace the lost volume or correct hypo-

albuminaemia, but whether intravenous albumin are beneficial or deleterious for patients with severe remains a matter of controversy (37). Some studies showed that albumin variation in early stage can be important risk factors for bad prognosis of severe AP (38). Using albumin in the treatment of severe AP may worsen the course and outcome of the disease (39), as it was shown in our study.

The present study has certain limitations that mainly lie in its design: due to incompleteness of retrospective data, the influence of some potentially relevant confounding variables on the observed outcome, such as existence and severity of chronic comorbidities, body mass index, etiology of acute pancreatitis, previous immunosuppressive therapy or the use of broad spectrum antibiotics before the onset of acute pancreatitis, as well as performed modalities of invasive treatment, could not be precisely assessed and therefore they were not included in the analysis; also, the cases and controls were not matched for potential confounders which would give a more accurate estimation of importance of investigated predictors of death due to severe necrotizing AP in the risk-set logistic regression model.

In conclusion, this study suggest that avoidance of albumin use in the absence of marked hypoalbuminemia and use of other colloid solutions in the initial fluid replacement could be beneficial for patients with predicted severe necrotizing acute pancreatitis in terms of reducing the risk of death, even in the cases of an increased risk according to Multiple Organ Dysfunction Score upon the admission to intensive care unit. Similar protective effects may also have an early introduction of enteral feeding, as well as the use of non-steroidal anti-inflammatory drugs and avoidance of octreotide use. However, further investigations, preferably in a prospective manner, are needed to determine the possibility of generalization of these findings, with an ultimate goal to improve prognosis of patients with severe acute pancreatitis and reduce the large overall burden of this disease on health system and society in general.

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The authors declare that they have no conflict of interest in this study.

References

1. Tenner S, Baillie J, Dewitt J, et al. American College of Gastroenterology. American college of gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013; 108: 1400-15. http://dx.doi.org/10.1038/ajg.2013.218

2. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62: 102-11. http://dx.doi.org/10.1136/gutjnl-2012-302779

3. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010; 139: 813-20. http://dx.doi.org/10.1053/j.gastro.2010.06.010

4. Doctor N, Agarwal P, Gandhi V. Management of severe acute pancreatitis. Indian J Surg 2012; 74: 40-6. http://dx.doi.org/10.1007/s12262-011-0384-5

5. Bradley EL III. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993; 128: 586-90. http://dx.doi.org/10.1001/archsurg.1993.01420170122019

6. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of complex clinical outcome.Crit Care Med 1995; 23: 1638-52. http://dx.doi.org/10.1097/00003246-199510000-00007

7. Schütte K, Malfertheiner P. Markers for predicting severity and progression of acute pancreatitis. Best Pract Res ClinGastroenterol 2008; 22: 75-90. http://dx.doi.org/10.1016/j.bpg.2007.10.013

8. Andersson B, Appelgren B, Sjödin V, et al. Acute pancreatitis - costs for healthcare and loss of production. Scand JGastroenterol 2013; 48: 1459-65. http://dx.doi.org/10.3109/00365521.2013.843201

9. Parsi MA. NSAIDs for prevention of pancreatitis after endoscopic retrograde cholangiopancreato graphy: ready for prime time? World J Gastroenterol 2012; 18: 3936-7. http://dx.doi.org/10.3748/wjg.v18.i30.3936

10. Khoshbaten M, Khorram H, Madad L, et al. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J GastroenterolHepatol 2008; 23: 11-6. http://dx.doi.org/10.1111/j.1440-1746.2007.05096.x

11. Sotoudehmanesh R, Khatibian M, Kolahdoozan S, et al. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol 2007; 102: 978-83. http://dx.doi.org/10.1111/j.1572-0241.2007.01165.x

12. Chan YC, Leung PS. Acute pancreatitis: animal models and recent advances in basic research. Pancreas 2007; 34: 1-14. http://dx.doi.org/10.1097/01.mpa.0000246658.38375.04

13. De Almeida JL, Jukemura J, Coelho AM, et al. Inhibition of cyclooxygenase-2 in experimental severe acute pancreatitis. Clinics (Sao Paulo) 2006; 61: 301-6. http://dx.doi.org/10.1590/S1807-59322006000400005

14. Dai HF, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. HepatobiliaryPancreat Dis Int 2009; 8: 11-6.

15. Aufenanger J, Samman M, Quintel M, et al. Pancreatic phospholipase A2 activity in acute pancreatitis: a prognostic marker for early identification of patients at risk. ClinChem Lab Med 2002; 40: 293-7.

http://dx.doi.org/10.1515/CCLM.2002.046

16. Mäkelä A, Kuusi T, Schröder T. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. Scand J Clin Lab Invest 1997; 57: 401-7. http://dx.doi.org/10.3109/00365519709084587

17. Nevalainen TJ. The role of phospholipase A2 in acute pancreatitis. Z Med Lab Diagn 1989; 30: 299-303. http://dx.doi.org/10.1007/bf01711349

18. Pezzilli R, Uomo G, Gabbrielli A, et al. A prospective multicentre survey on the treatment of acute pancreatitis in Italy. Dig Liver Dis 2007; 39: 838-46. http://dx.doi.org/10.1016/j.dld.2007.05.014

19. BasurtoOna X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev 2013; 7: CD009179. http://dx.doi.org/10.1002/14651858.cd009179.pub2

20. Marshall JC. The Multiple Organ Dysfunction (MOD) Score. Sepsis 1997; 1: 49-52. http://dx.doi.org/10.1023/A:1009715402392

21. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut 2004; 53: 1340-4. http://dx.doi.org/10.1136/gut.2004.039883

22. Petrov MS, Zagainov VE. Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: a systematic review. ClinNutr 2007; 26: 514-23. http://dx.doi.org/10.1016/j.clnu.2007.04.009

23. Wang G, Wen J, Xu L, et al. Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. J Surg Res 2013; 183: 592-7. http://dx.doi.org/10.1016/j.jss.2012.12.010

24. Marik P, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. IntCare Med 2004; 30: 748–56. http://dx.doi.org/10.1007/s00134-004-2167-y

25. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo ClinProc 2003; 78: 1471–8. http://dx.doi.org/10.4065/78.12.1471

26. Tang WF, Wang YG, Zhu L, et al. Effect of somatostatin on immune inflammatory response in patients with severe acute pancreatitis. J Dig Dis 2007; 8: 96-102. http://dx.doi.org/10.1111/j.1443-9573.2007.00293.x

27. Wang G, Wen J, Wilbur RR, Wen P, Zhou SF, Xiao X. The Effect of Somatostatin, Ulinastatin and Salvia miltiorrhiza on Severe Acute Pancreatitis Treatment. Am J Med Sci 2013; 346: 371-6. http://dx.doi.org/10.1097/MAJ.0b013e31827aa2bc

28. Uhl W, Büchler MW, Malfertheiner P, et al. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. Gut 1999; 45: 97-104. http://dx.doi.org/10.1136/gut.45.1.97

29. Cavallini G, Frulloni L. Somatostatin and octreotide in acute pancreatitis: the never-ending story. Dig Liver Dis 2001; 33: 192-201. http://dx.doi.org/10.1016/S1590-8658(01)80077-3

30. Wall I, Badalov N, Baradarian R, et al. Decreased mortality in acute pancreatitis related to early aggressive hydration. Pancreas 2011; 40: 547-50. http://dx.doi.org/10.1097/MPA.0b013e318215368d

31. De-Madaria E, Soler-Sala G, Sánchez-Payá J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. Am J Gastroenterol 2011; 106: 1843-50. http://dx.doi.org/10.1038/ajg.2011.236

32. Trikudanathan G, Navaneethan U, Vege SS. Current controversies in fluid resuscitation in acute pancreatitis: a systematic review. Pancreas 2012; 41: 827-34. http://dx.doi.org/10.1097/MPA.0b013e31824c1598

33. Zhao G, Zhang JG, Wu HS, et al. Effects of different resuscitation fluid on severe acute pancreatitis. World JGastroenterol 2013; 19: 2044-52. http://dx.doi.org/10.3748/wjg.v19.i13.2044

34. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid

resuscitation in intensive care. N Engl J Med 2012; 367: 1901-11.
http://dx.doi.org/10.1056/NEJMoa1209759

35. Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. Pancreatology 2009; 9: 770-6.
http://dx.doi.org/10.1159/000210022

36. De-Madaria E. Latest advances in acute pancreatitis. GastroenterolHepatol 2012; 35(suppl 1):98-101.
http://dx.doi.org/10.1016/S0210-5705(12)70041-9

37. Caraceni P, Domenicali M, Tovoli A, et al. Clinical indications for the albumin use: Still a controversial issue. Eur J Intern Med 2013; 24: 721-8.
http://dx.doi.org/10.1016/j.ejim.2013.05.015

38. Chen Y, Zhang ZW, Wang B, et al. Relationship between early serum albumin variation and prognosis in patients with severe acute pancreatitis treated in ICU. Sichuan Da XueXueBao Yi Xue Ban 2013; 44: 237-41.

39. Xue P, Huang ZW, Li YH, et al. Clinical study on severe acute pancreatitis associated with hypoalbuminemia in early stage. Zhong Xi Yi Jie He XueBao 2005; 3: 443-5.
http://dx.doi.org/10.3736/jcim20050606

Analiza faktora udruženih sa smtrnim ishodom kod pacijenata sa teškim nekrotičnim akutnim pankreatitisom

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SAŽETAK

Cilj ove studije bio je da utvrdi faktore u vezi sa inicijalnom terapijom koji mogu doprineti smrtnom ishodu kod bolesnika sa teškim nekrotičnim akutnim pankreatitisom i da analiziraju njihov klinički značaj, kao i moguće aditivno dejstvo.

Sprovedena je retrospektivna studija tipa "slučaj-kontrola", u koju su uključeni svi punoletni bolesnici lečeni zbog teškog nekrotičnog akutnog pankreatitisa u Kliničkom centru "Kragujevac" tokom petogodišnjeg perioda (2006-2010). "Slučajevi" (n=41) su bili bolesnici koji su umrli zbog pomenutog oboljenja, dok su kontrolnu grupu (n=69) činili bolesnici kod kojih smrtni ishod nije zabeležen. Da bi se procenila povezanost između potencijalnih faktora rizika i opserviranog ishoda, pomoću logističke regresione analize računati su sirovi i korigovani unakrsni odnosi šansi (OR) sapripadajućim 95% intervalom poverenja (CI).

Značajna povezanost sa smrtnim ishodom pokazana je za primenu preparata želatina i/ili hidroksietil-skroba (korigovani OR 12,555; 95% CI 1,150-137,005), primenu albumina (korigovani OR 27,973; 95% CI 1,741-449,373), primenu oktreotida (korigovani OR 16,069; 95% CI 1,072; 240.821) i izostajanje rane enteralne ishrane (korigovani OR 3,933; 95% CI 1,118-13,829). S druge strane, primena nestroidnih antiinflamatornih lekova imala je zaštitnu ulogu (korigovani OR 0,057, 95% CI 0,004-0,805).

Rizik od smrtnog ishoda kod bolesnika sa teškim nekrotičnim akutnim pankreatitisom može se značajno umanjiti izbegavanjem rane primene koloidnih rastvora, albumina i oktreotida, kao i ranim uvođenjem oralne/enteralne ishrane i primenom nesteroidnih antiinflamatornih lekova.

Ključne reči: pankreatitis, **akutni nekrotički, faktori rizika, smrtni ishod, albumini**