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FIELD OF MEDICINE

LIMITS AND POSSIBILITIES OF INTENSIVE MANAGEMENT IN THE TREATMENT OF SHOCK AND ITS COMPLICATIONS IN SEVERE ACUTE PANCREATITIS

DOCTORAL THESIS ABSTRACT

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Introduction

Severe Acute Pancreatitis (SAP) is a life-threatening condition with sudden onset and major impact on the body. The incidence of this disease in the last decades is constantly increasing due to living conditions and risk factors such as unhealthy diet and alcohol consumption.

PAS shock is a fight against time, requiring advanced and complex life support. The course of the disease is uncertain, that is why it is important to establish serum markers to rapidly detect patients prone to the severe form and complications of PAS according to: etiology, age, comorbidities, temporal phase of pancreatitis. Therapy trends are continuously changing, therapeutic artifices and recommendations to resolve organ dysfunction are challenging. The good condition of a patient with AP on admission, can rapidly progress to the severe form, and multiple complications may occur. It is important to apply effective treatment and eradicate risk factors so that the patient's rehabilitation is complete and recurrent episodes of AP or disability do not occur.

SBP is a burden on the healthcare system and has a socio-economic impact, considering the costs of hospitalization of a patient in ICU. The quality of life after this can also be poor. Sequelae of muscle strength, neuropathies, reversal of circadian rhythm, the need for psychological support, the patient needing reintegration into the field, can occur.

The PhD thesis aims to contribute to the already existing literature, through a common denominator between the medical knowledge of anesthesia and intensive care, and general surgery, combining known but also innovative notions of public health problems, bringing an improvement in the management of PAS and shock in this pathology.

The study realized in the framework of the thesis, was carried out at the University Emergency Hospital of Bucharest and presents the ways to identify the severity of AP, the monitoring of shock in AP, and the specific IT treatment modalities: volemic repletion, nutrition, analgesia, extracorporeal extracorporeal epuration, constituting a topic of national interest, innovative.

Current state of knowledge

Acute pancreatitis is the pathological entity due to acute inflammatory reaction of the pancreas, a complex lesional process, which can have variable impact and repercussion: either localized to the pancreas, or extended to peripancreatic, retroperitoneal tissues, organs distant from the pancreatic lodge, or systemic [1].

At the 2012 Atlanta Congress in 2012, the definition of the disease and the classification of forms according to severity were revised, thus optimizing the diagnosis, management, standardization of reported cases, and prognosis of the condition[1][2].

In Europe, the incidence is 40 - 50 cases per 100,000 inhabitants, being higher in Eastern European countries [4]. Data from the Global Burden of Disease study revealed a global incidence rate of pancreatitis of 5,210,000 patients in 2016, representing a 30% increase compared to the incidence in 2006[5] In Romania, there are no data on the incidence of AP.

The diagnosis of AP requires at least two of the following three features: abdominal pain, with epigastric "bar" epigastric site with posterior irradiation and at least threefold elevated blood levels of lipase or amylase or characteristic changes of the disease on contrast-enhanced computed tomography, and less frequently on nuclear magnetic resonance or abdominal ultrasonography [82,3]. When increases in lipase and/or amylase are inconclusive, computed tomographic examination is absolutely necessary. [3]

PAS is characterized by the occurrence of persistent organ failure lasting more than 48 hours, irrespective of the time of development in relation to the onset of disease, or by the presence of local complications: fluid collections, pseudocyst, sterile or infected peripancreatic necrosis as well as closed necrosis,walled-off necrosis (WON), sterile or infected.

II.Personal contributions

The survival duration of PAS, according to the Atlanta classification, and the determinant-based classification, is inversely proportional to the intensity of systemic shock caused by persistent SIRS and cytokine storm. As a result, it is paramount to diagnose the disease as early as possible and to categorize the severe form in order to achieve optimal treatment and patient monitoring in IT.

Thus, the first study in this thesis aims to identify patients at risk of developing the severe form of AP, comparing the prognostic rate according to several indices and severity scores, since admission, the first set of biological analysis and imaging evaluation. We aim to highlight the means to avoid the transition from transient to permanent SIRS, and the development of organ dysfunction.

We will investigate which types of etiologies have predominantly higher morbidity, risk factors and patient-associated comorbidities correlated with the number of ventilator days, ICU admission, occurrence of local and systemic complications and mortality rate.

We also want to assess the reliability between existing severity scores, their sensitivity and specificity, predicting not only severity but also the number of ventilator days and death rate.

Also to signal severity from hospitalization, we compared novel inflammatory markers, such as presepsin, procalcitonin, CRP, lactate, neutrophil/lymphocyte ratio, which correlate better with MV days, ICU hospitalization days, complications, death.

The second study of the thesis follows the therapeutic management of PAS. We analyzed hydroelectrolyte rebalancing, quantitatively and qualitatively, using dynamic parameters SVV, PPV, improving prognosis and reducing complications- such as renal injury, prolonged mechanical ventilation, abdominal compartment syndrome, death rate. Four groups were compared by fluid type: saline, balanced fluid, human colloid, and synthetic.

Another second aim, was the approach of nutrition and correlation of the type of nutrition: oral enteral, parenteral, mixed, their correlation with outcome, noting complications occurred. Then we compared multimodal analgesia by dividing it into 4 groups:

predominantly thoracic epidural catheter analgesia, opioid-based analgesia, predominantly NSAID analgesia, and mixed with synthetic opioid medium dose.

The study also showed the prognostically beneficial importance of plasmapheresis in hypertriglyceridemic SBP, and cytokine-filtered hemodiafiltration in SBP shock.

Based on the collected data and the multitude of algorithms, we aim to optimize the management of ICU patients with SBP.

We conducted an observational, retrospective study of 161 patients hospitalized with the diagnosis of PAS, in the Anesthesia and Intensive Care Clinic of the University Hospital of Bucharest. The inclusion period was from October 1, 2014 to May 15, 2022.

The patients were clinically, biologically and imaging evaluated at inclusion in the study, subsequently their evolution was followed with the aim of transfer to the ward, then at and discharge from the hospital or evolution to death.

Inclusion criteria for the study were:

- Age over 18 years

- Patients domiciled in Romania

- Patients with diagnosis and criteria of PAS according to the modified Atlanta 2012 definition or critical form according to the determinant-based definition.

- Hospitalization in ICU during the study period to observe the current therapeutic possibilities and limitations.

Data collection was performed from October 1.2014 to May 15.2022, and data processing thereafter.

For statistical data processing we used SPSS (statistical package for Social Sciences) program version 25.

We created a retrospective study, realized by studying the evolution of the patient with PAS. We admitted to the study patients aged between 18 and 95 years, who met the criteria Bisap > 2 and Apache II > 8, or Bisap > 2 and Ranson > 3 at 7 and 48 hours. All patients included in the study had systemic inflammatory response syndrome (SIRS) and were diagnosed with AP presenting at least two of three criteria and severity criteria. We identify which etiologic forms correlate with high complication or death rates.

In our cohort, out of 161 patients, 54 met the criteria for critical AP, and 87 had multiple organ dysfunction for more than 48 hours.

The early and late local complications were 1.acute necrotic collections 89 patients-(55.3%), 2. undelimited necrosis 47-29.2(%), 3. IFN 32 (19.9%), 4. pseudocysts 28-(17.4%), 5. compartment syndrome 23-(14. 3%), 6. won 23-(14.3%), 7. peritonitis-10 (6.25%). After surgery, and as a result of systemic and local and systemic complications occurred, the mortality rate was 47.8% .

The systemic complications were: 78 patients had cardiac complications (48.8%): acute myocardial infarction, rhythm disturbances, decompensation of heart failure, 158 (98.8%)-SIRS persistent, 154-(96.3%) pulmonary with oxygen requirement for a paO2>60 mmhg, renal 134-(83.8%) with aggressive volemic repletion requirement and later in the de-escalation phase, ansa diuretic. Neurologic complications in 65 patients (40.6%) were: agitation confusion, agitation, delirium, psychosis, withdrawal, encephalopathy.

The Charlson comorbidity index is intended to indicate patients more likely to have a poor prognosis, with 0 index meaning no comorbidities, 1=one severe underlying disease with a chance of exacerbation, 2=two severe underlying diseases, and 3 > three severe, coexisting diseases of the patient. [305]

Of the patients 81 were female and 80 were male, 51% versus 49%.

Thus according to age range between 61-70 years of age there were 32 patients. Followed by range 51-60- 31 patients subsequently 41-50 years 30 patients.

The research group consisted of 161 patients, out of which 80(49.7%) patients were male, which indicates the lack of gender prevalence in this type of condition$\chi 2(1)= 0.006$ and p<0.01.

112 of the patients (69.6%) were from urban setting. Out of 161, 150 patients (93%) had no relapses following treatment, 9 patients had one relapse and two had multiple relapses.

Among the etiologies, the most frequent etiology was biliary: 40 patients, then ethanolic - 39 patients, followed by hypertriglyceridemic - 28 patients, idiopathic - 22, hypoperfusion - 18, mixed - 6 patients who had criteria for both ethanolic and biliary PAS, 2 patients had biguanide treatment, one patient with ACEI and one with valproic acid, considering it as a drug cause.

In terms of etiology, biliary (24.8%) and ethanolic (24.2%) etiologies were highly weighted, followed by hypertriglyceridemic (17.4%), idiopathic (13.7%) and hypoperfusion/ischemia (11.2%).

A major, statistically significant difference was identified between the distribution of etiologies by gender, $\chi^2(6)=15.01$ și $p<0.05$, in that for men the predominant etiology was ethanolic (33.8%) while for women the major etiology was biliary (32.1%).

The ages of the patients ranged from 18 to 95 years, with a median value of 56 years and a Q1 - Q3 quartile range between 45.5 and 69.5 years. The distribution is approximately symmetric for a normality test value (Kolmogorov-Smirnov) K-S=0.045 and p>0.200. Mortality is high, the observed proportion was about 48% (47.8%), we can consider the probability of death about 50%, $\chi^2(1)=0.30$ și $p>0.01$,, this is due to patients in shock in the ICU.

No differentiation in mortality by gender was identified.

Analysis of the relationship between age, mortality and age and ICU day stay. ROC analysis indicated a statistically significant critical value of age (>47 years) for a statistically significant AUC=.706 (CI95%: .630 - .776), Ztest=5.11 and p<.001. The determined critical value has a sensitivity Sn=85.71 and a specificity Sp=45.24. The confidence interval of the critical value is between 39 and 64 years.

In our study a high proportion of comorbidities (84.5%) and also of patients with at least three comorbidities (47.7%).

Individually, the main types of diseases are in order of frequency, in first place cardiac (34.8%), then in second place diabetes, hypo/hyperthyroidism (35.4%), followed by obesity (22.4%), vascular (20.5%), digestive (19.9%), pulmonary (16.8%), neoplastic (17.4%) . 11.2% of the patients in the described group presented metabolic disorders, such as metabolic syndrome or hypertriglyceridemia (11.2%).

The presence of comorbidities was associated with a ratio of occurrence of death about 2.6 (CI95%: 1.01 - 6.61) times higher than in the absence of comorbidities, statistically significant ratio for Wald(1)=3.87 and p<0.05.

Of the comorbidities, cardiovascular and digestive (cirrhosis of the liver) comorbidities have a chance of death about 3 times (exp(B)=3.11; CI95%: 1.37 - 7.07), respectively 3.5 times (exp(B)=3.50; CI95%: 1.50 - 8.17) higher than those without these types of conditions for Wald values = 7.32 - 8.42 and a significance level p<0.01.

The Mann-Whitney non-parametric comparative Mann-Whitney analysis resulted in a significant difference between the median age level of survival (md=51.0) Q1 - Q3 (38.0 -

64.0) and the median level of death (md=65.0) Q1 - Q3 (51.0 - 75.5) for a standardized Z-test value of Z=4.43 and p<0.001.

We compared the four most common types of analgesia for all time points (2, 6, 24 and >48 hours). The lowest pain scores were obtained for epidural catheter, 95% of patients had scores below the median value. Only 36 patients (22.4%) receive epidural catheter. The median duration of epidural analgesia was 5.5 days.

Patients receiving analgesia on KP required minimal additional NSAIDs. Among the complications of multimodal analgesia the presence of large gastric aspirate with cessation of nutrition, functional ileus and mild hypotension accentuation without increased norepinephrine (87.0%) but requiring fluid bolus were more frequent.

Of patients who received plasmapheresis (24), 85% survived and 15% died, and of those who had conservative treatment (18), 47.5 survived and 52.5% died.

Conclusions

The present thesis is composed of several researches on PAS, having a difficult topic, as there is currently no consensus on the prevention, staging, management of shock in PAS and complications of the disease.

The objectives of the study are of both general and national interest, constituting a topical issue, involving specialties such as anesthesiology and intensive care, general surgery and gastroenterology.

In the 161 patients studied, we observed that the main risk factors in AP were age and the presence of comorbidities.

We concluded that, for the age range 50-60 years, the death occurrence ratio is about seven (p<0.01) times higher than in patients up to 40 years of age.

In our study, among the most frequent systemic complications were cardiac complications (tachyarrhythmias, CHF decompensation, hypo/hypertension, ESV), and they were more frequent in the 35-64 years age range. Cardiac events in these patients were associated with a high survival rate of 78%. They were also the result of continuous

hemodynamic and electrocardiographic monitoring, with the ICU proactively managing biological imbalances, leading to increased survival. If CCI>2 the chance of developing a cardiac complication increases. The older the patients, the greater the impact of new-onset cardiovascular disease. The results of our study found that for the young hospitalization was less than five days and for the elderly it was higher. Over 70 years of age the ratio of occurrence of death increases greatly (p<0.001) compared to those aged 40 years and under.

For patients aged 35-65 years, we correlated the results with higher hospitalization and higher risk of local complications: CNA, pseudocyst, WON.

In the elderly, we encountered the phenomenon of prolonged weaning, a period of more than five days in which the ventilatory parameters are not successfully lowered and uncoupling from it and oxygenation with the T-piece (55.7%).

The presence of comorbidities is associated with a ratio of occurrence of death about 2.6 times higher than in the absence of comorbidities, statistically significant ratio for Wald(1)=3.87 and p<0.05.

Of the comorbidities, cardiovascular comorbidities have a chance of death about three times and 3.5 times higher, respectively, than those without these types of conditions, for Wald values = 7.32 - 8.42 and a significance level p<0.01.

It was identified that metabolic syndrome/hypertriglyceridemia has a protective effect, if the rank of comorbidities=1. The odds ratio of survival is about 2.7 (/1/exp(B)=.37) times lower, than those with other comorbidities, due to the implementation of plasmapheresis in the management of SBP.

The serologic markers of severity investigated predicting the rate of complications or death were NLR, P-SEP, procalcitonin, lactate, CRP. High values of P-SEP>1000 correlated with the number of organ dysfunctions occurred in the course of AP. All cases of necrotizing infection were faced with an increase in P-SEP again, compared to the value at admission.

Presepsin and C-reactive protein values for those who died were in high proportion 72/74 higher than the median value of the distribution.

It is observed that patients with procalcitonin 2-10 are mostly those with extra-pancreatic complications (57.3%), such as those with septic shock with pulmonary end point, pneumonias. And patients with high procalcitonin (>10), but without criteria of infection with

pulmonary tropism or blood torrent (negative blood cultures) were IFN patients. When procalcitonin level exceeded 10 the most frequent complications were IFN (81.7%).

As for the procalcitonin value, without clinical examination of the patient, this taken as a value does not differentiate on the basis of a bifactorial model extra-abdominal septic shock from IFN.

For Lactate the ROC analysis indicated a statistically significant critical value (>2) for AUC=0.764 (CI95%:0.691 - 0.828), Ztest=7.15 and p<0.001. The critical value determined, has a sensitivity Sn=63.64 and a specificity Sp=76.19. The confidence interval is between 1.7 and 3, to determine the severity of PA.

For PCR the ROC analysis indicated a statistically significant critical value (>150) for AUC=0.791 (CI95%: 0.720 - 0.851), Ztest=7.84 and p<0.001. The determined critical value has a sensitivity Sn=71.43 and a specificity Sp=85.71. The confidence interval of the critical value, signaling the severity of AP, is between 70 and 160. For PCR greater than 150 the sensitivity for complications is 71% and specificity 85%, and a lactate value greater than 2 is associated with higher rate of death.

Looking for the reliability of severity scores we obtained the results:

ROC analysis indicated a statistically significant APACHE (>21) critical score value of AUC=0.925 (CI95%: 0.872 - 0.960), Ztest=21.04 and p<0.001. The determined critical value has a sensitivity Sn=87.01 and a specificity Sp=83.33. The confidence interval of the critical value is between 20 and 25 score points.

Binary logistic logistic regression analysis indicates a statistically significant pattern based on BISAP score for a Wald value=27.22 and p<0.001, the chance of death is 5.24 times higher in BISAP=4, and 9.83 times higher in BISAP=5 than BISAP=3.

Calculating the cumulative RANSON score, we obtained a Wald value = 49.14 and p<0.001, the chance of death is 19.91 times in the case of RANSON=7 and very high in the case of RANSON>7 compared to RANSON=6.

From the comparison analysis of the amount of organ dysfunction sum, according to the level of severity of acute pancreatitis, a statistically significant difference was identified for a median comparison test value ($\chi2$=6.48 și p<0.05), in the sense that a lower Sofa score corresponds to a better prognostic value, which also correlates with the CT index severity index.

Investigating the outcomes of shock management in PAS, we concluded data on repletion, nutrition, analgesia, plasmapheresis, CVVHDF with cytokine filter.

In composing an appropriate treatment, in fluid management, the study answered topical questions, such as how much and what type of fluid is needed in optimal rebalancing of SBP, and the use of SRL, correlated with a favorable prognosis, with an improvement in outcome, metabolic acidosis and base deficiency. A protective effect (B=-0.97) was observed for the use of SRL, with a 2.6-fold higher odds ratio for survival than for non-use (1/Exp(B)=1/0.38=2.61).

A worsening effect was observed in the case of synthetic colloid use (B=-0.97), with a 2.7-fold higher odds ratio of death than in the case of use (Exp(B)=2.67).

For ACS, the statistically significant pattern is that based on aggressive resuscitation (Wald=3.06; df=1; p=0.080<0.01). The use of high fluid rates is associated with an odds ratio of about four times higher chance of ACS than the mean rate (B=1.4; exp(B)=4.04).

Surgical intervention for acute abdomen and performing emergency laparotomy, was preponderantly, following aggressive volemic resuscitation, in most cases associated with albumin use (Wald=5.04; df=1; p=0.080<0.01). Abumin use, was associated with an approximately twice higher odds ratio of surgery for compartment syndrome, than no use (B=.73 exp(B)=2.07).

We conclude that albumin has no role in the volemic resuscitation of PAS, its use being associated with twice the risk of patients developing abdominal compartment syndrome. Of the complications associated with aggressive fluid repletion, the most frequent were: pulmonary complications: n=134 (83.2%): ARDS, and respiratory dysfunction associated with EVLW >11 ml/kg, cardiovascular complications: n=13 (8.1%), renal complications 5: n=18 (11.2%). No statistically significant associations between fluids and neurologic complications were identified.

There was a statistically significant pattern of predicting death (Wald=11.27 and p<0.001) when using EN, meaning a 3.33 times greater chance of survival compared to total parenteral nutrition. EN is significant and associated with higher survival rate and decreased hospitalization in the ICU compared to NP.

NE, compared with PN, is more frequently associated with pneumonia, bronchopneumonia or VAP, 1.90 times more likely to have respiratory complications such as those mentioned (AK3,4) (B=0.64; exp(B)=1.90).

For PN the relationship is not statistically significant for pulmonary complications.

For blood glucose variations, between enteral and parenteral nutrition, there is no statistically significant difference. We found that for PN when using the bottle without glucose compartment is associated with a 2.38 times lower chance of death (Wald=3.33; p=0.068) compared to patients who had complete total parenteral nutrition.

In terms of analgesia, those without an epidural catheter were 27 times more likely to receive more opioids (B=3.29; exp(B)=26.84

The lowest pain scores were obtained with epidural catheter, for which at least 95% of patients have scores below the median value. We demonstrated the tolerability effect and the need for multimodal analgesia in opioid patients with a combination of NSAIDs or other classes of analgesics.

Patients receiving KP required minimal NSAID supplementation and had minimal complications. Patients who did not benefit from epidural catheter, had high opioid requirements, with a 28-fold increased risk of large gastric aspirate, >500ml, with EN compromise. Ileus at 48h was present in 54.7% of patients without KP analgesia.

Mild accentuation of hypotension without increasing vasopressor rate (87.0%) was frequently encountered in patients with KP analgesia, necessitating fluid bolus, or rate modification of continuous analgesia on the injectomat.

KP analgesia was associated with a lower incidence of IFN. From the binary logistic regression logistic regression analysis of the occurrence of the local complication undelimited necrotizing necrosis according to epidural catheter use, a lower chance of IFN occurrence was observed in those with epidural catheter (B=-0.89; exp(B)=0.41; 1/exp(B)=2.44).

48% of patients with KP analgesia had no complications, 16% had local discomfort, 4% motor block, 16% KP dislocation, 4% .

KP constitutes the optimal analgesia in PAS and should be implemented proactively whenever possible to avoid opioids and their complications.

Continuous cytokine-filtered renal replacement therapy correlates with higher survival rate and decreased acidosis and cardiocirculatory support in shock in PAS.

From the binary logistic regression analysis of admission acidosis according to the use of cytokine-filtered CRRT, statistically significant differentiation(Wald=6.44; p=0.011) and a lower chance of worsening of acidosis in those with cytokine-filtered CRRT, but also a stagnation of vasopressor requirement to support mean pressure(B=-1.61; exp(B)=0.20; 1/exp(B)=5.00). Looking at acidosis and its trend according to the use of CRRT, statistically significant differentiation (Wald=18.62; p=0.001) and a higher chance of improvement of acidosis in those with CRRT and cytokine filter (B=-2.42; exp(B)=0.09; 1/exp(B)=11.10).

There was no statistically significant difference in VM days by use of CRRT with cytokine filter or death rate.

Plasmapheresis depletes blood triglycerides and is associated with significantly better survival. In the case of plasmapheresis, the presence of plasmapheresis is statistically significant protective (Wald=8.00 and p<0.01), the chance of not having death is 6.25 times lower (B=-1.83; 1/exp(B)=1/0.16) than without plasmapheresis in hypertiglyceridemic pancreatitis.

Thus the research objectives that I set out to be resolved in the thesis were realized.

I identified risk factors for patients with PAS and described the prognostic relevance of existing severity scores and inflammatory markers.

We exposed the correlation between IFNs and procalcitonin. We emphasized the importance of volemic repletion, nutrition, prognostic relevance of progression and its complications by type and duration.

We described the importance of KP analgesia, prevention of IFN with its fitting, decrease of bacterial complications and faster ICU and hospital discharge.

We established the prognostic relevance, the use of plasmapheresis for triglycerides greater than 999 mg/dl, and extracorporeal cytokine filter extracorporeal cytokine filtering in patients with AKI, instability and severe acidosis, correlating with lowering of triglycerides and better prognosis.

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