THE EVOLUTION OF THE VALUES OF PROCALCITONIN AND INTRA-ABDOMINAL PRESSURE IN SEVERE ACUTE PANCREATITIS

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Abstract: *Severe acute pancreatitis (SAP) is one of the main causes of intra-abdominal hypertension (IAH). SAP mortality remains high, between 15% and 30% and is the result of infection of pancreatic necrosis and multiple system organ failure (MSOF). Early recognition of increased intra-abdominal pressure is essential in the management of acute pancreatitis and may reduce the morbidity and mortality associated with this disease. Procalcitonin (PCT) is an indicator that identifies sepsis and also an important marker of severe forms of acute pancreatitis. Research is directed towards finding a single marker that can be quickly measured, in a repeated way, cheap and without leading to discomfort in patients. This study compares the maximum values of PCT and intra-abdominal pressure (IAP) in the patients with acute pancreatitis.*

INTRODUCTION

Mortality in SAP remains high between 15% and 30 % and it is the consequence of infected pancreatic necrosis and MSOF.(1,2,3) The elevation of intra-abdominal pressure after the onset of pancreatitis is of increasing interest. The intra-abdominal compartment syndrome, which may appear in acute pancreatitis is associated with MSOF, with a reserved prognosis and high mortality rate.(3,4,5,6)

Procalcitonin is a marker used for severe bacterial and fungal infections (32), an important indicator to identify sepsis and also an important marker to identify severe forms of acute pancreatitis.(7) Values of procalcitonin between 2 and 10 ng/ml involve the presence of sepsis, with a high risk of evolution towards severe sepsis. Procalcitonin values above 10 ng/ml indicate the presence of severe sepsis or septic shock.(8) In acute pancreatitis, it allows the identification of severe forms and helps distinguishing between sterile necrosis and the infected type.(9)

PURPOSE

The aim of this prospective study is to compare serum values of procalcitonin (PCT) with intra-abdominal pressure (IAP) and to establish the existence of a correlation between these markers in the evolution of severe acute pancreatitis.

The study aims at comparing maximum values of PCT and IAP in 48 patients with acute pancreatitis and correlating them with the emergence of severe complications and mortality rate.

MATERIALS AND METHODS

The study was approved by the Ethics Board of The Clinical Emergency County Hospital, Sibiu.

From January 2011 to April 2014, a group of 48 patients admitted to the Clinical Department of Anasthetics and Intensive Care and in the surgical departments (Surgery I and Surgery 2) of the Clinical County Emergency Hospital, Sibiu, being diagnosed with acute pancreatitis, was included in this prospective, observational study.

Grading the types of pancreatitis according to the severity index was performed by observing the Atlanta criteria and more specifically a criterion or several of the following:

- Ranson score on admission ≥ 3 (repeated after 48 hours);
- Apache II score ≥ 8 (anytime during the progression of disease);
- The presence of SIRS or of one or more dysfunctions/ organ failures;
- The presence of one or several local complications (pancreatic necrosis, pancreatic pseudocyst or abscess).

The pancreatic infection was confirmed by means of bacteriological test of the collected liquid by means of fine-needle puncture – aspiration or performed during surgery.

The intra- abdominal pressure was measured every 24 hours and the maximum value was used to compare the maximum serum values of procalcitonin.

Intra-abdominal pressure (IAP) was measured through the technique described by Kron et. al.(10) In order to determine intra-abdominal pressure, a catheter set up into the bladder was used, connected to a pressure transducer. 50 ml of saline was instilled into the urinary bladder and the pubic symphys was considered as level 0. IAP maximum was considered the highest pressure obtained at all measurements.

Serum procalcitonin was measured using the semiquantative Brahms method, on admission, after 24 hours, after 48 hours, on day 8 and 10 from admission and once again repeated during the fourth week from admission. In the present study, BRAHMS PCT – Q kits were used, an immunochromatographic test for the semiquantitative detection of PCT. It is a fast method, with available results in 19 minutes.

Interpretation:

- PCT < 0,5 ng/ml – Normal values
- PCT 0,5 - 2 ng/ml –Moderate Systemic Inflammatory Response (SIRS), infection as a cause is probable; It may be caused by a trauma, cardiogenic shock, surgical trauma.
- PCT 2 – 10 ng/ml – Severe systemic inflammatory response (SIRS), most likely caused by systemic infection and sepsis, with or without organ failure.
- PCT > 10 ng/ml – Intense systemic inflammatory response due to bacterial shock or a septic shock.

The statistical analysis has been performed using

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SPSS (Statistical Package for the Social Sciences) version 15.0, Chicago. The patients were divided into two groups: those with mild acute pancreatitis (MAP) and those with severe acute pancreatitis (SAP) according to the Atlanta classification criteria. The variables were referred to as absolute numbers and percentages. The statistical work was performed by means of *t* student, Mann - Whitney *U* and Chi square tests. The results of statistical tests were presented, where applicable, with a confidence interval of 95%. A value $p < 0,05$ was statistically considered.

RESULTS

A total number of 48 patients (28 males and 20 women) with acute pancreatitis were included in our study, ages ranging from 21 to 69 years old. Those 48 patients had ages ranging between 21 and 69 years old, the mean age of the group was 45 years old (21-69 years).

Out of the total of 48 cases, 23 (47, 91%/) patients presented mild forms of pancreatitis and 25 (52, 08%) cases with severe acute pancreatitis.

The grading according to the severity index was performed by observing the Atlanta criteria.

Table no. 1. Complications of the 48 patients with acute pancreatitis

	MAU (n = 23)	SAP (n = 25)	Total	*P value*
Local complications	2 (8.7%)	25 (100%)	27 (56.2%)	< 0.001
Multiple organ and system failure	0	24 (96%)	24 (50%)	< 0.001
Pancreatic necrosis	2* (8.7%)	25(100%)	27 (56.2%)	< 0.001
Extended Pancreatic necrosis	0	8 (32%)	8 (16.6%)	0.005
Infected Pancreatic necrosis	0	12 (48%)	12 (25%)	< 0.01
Sepsis	0	12 (48%)	12 (25%)	0.02
Mortality	0	7 (28%)	7 (15%)	0.01

*MAU, mild acute pancreatitis; SAP severe acute pancreatitis; *pancreatic necrosis 30% or less;*
The P value was calculated using Chi square test.

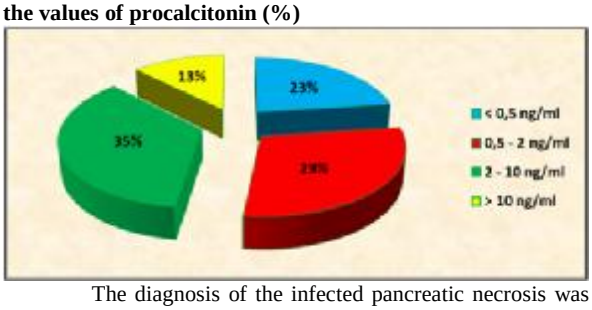
The SAP patients had at least one organ failure during hospitalization (table no. 1). All patients with SAP presented pancreatic local complications. The mortality rate was 15 % and was recorded in the SAP group (table no. 1). 24 (96%) of patients with SAP developed MSOF during the course of disease. The incidence of pancreatic necrosis, of extended pancreatic necrosis and of infected necrosis was illustrated in table no. 1. The extension of pancreatic necrosis was highlighted by means of contrast enhanced CT. The maximum IAP measured values were compared to the maximum serum levels of procalcitonin (PCT), to the emergence of complications and mortality rate.

Out of the 25 patients with SAP, 12 (48%) patients presented infected pancreatic necrosis and sepsis, severe sepsis or septic shock. Out of the patients with infected pancreatic necrosis, 6 patients presented severe sepsis and 6 patients presented septic shock. In patients with severe sepsis, the values of procalcitonin ranged between 2- 10 ng/ml, and in patients with septic shock, the values of procalcitonin were> 10 ng/ml.

Table no. 2. The division of acute pancreatitis depending on the values of procalcitonin

Procalcitonin	No. of cases
< 0.5 ng/ml	11 (22.91%)
0 .5 - 2 ng/ml	14 (29.16%)
2 - 10 ng/ml	17 (35.41%)
>10 ng/ml	6 (12.5%)

Figure no. 1. The division of acute pancreatitis depending on the values of procalcitonin (%)



The diagnosis of the infected pancreatic necrosis was checked through computed tomography (CT) ("bubble gas" aspect), puncture aspiration, the serum level of procalcitonin and confirmed through bacteriological examination of the liquid obtained through puncture aspiration or during the time of the operation.

In all the patients with infected necrosis, surgical intervention was performed.

Patients with severe acute pancreatitis received antibiotics as treatment (Meropenem or Imipenem). 21 patients with SAP needed surgical intervention, 12 patients with infected pancreatic necrosis and 9 patients with sterile necrosis. The operated patients received antibiotheraphy before and after the operation. All the patients with SAP, with antibiotherapy received accompanying antimicotics (Fluconaxol, Voriconazol or Ecalta, depending on indications). Some patients with severe sepsis, septic shock or severe septic complications (colon perforation, postoperative fistula) needed antibiotic associations (for example, Meropenem or Imipenem with Vancomicyn or Linezoid) according to the antibiogram.

From the point of view of intra-abdominal pressure, the acute cases of pancreatitis from our case-studies were divided into IAP pancreatitis < 12 mmHg and intra-abdominal hypertension cases of pancreatitis, with IAP $\geq$ 12mmHg, out of which with IAP > 20 mmHg and organ dysfunction being included into the clinical severe forms with abdominal compartment syndrome(ACS), with a reserved prognosis.

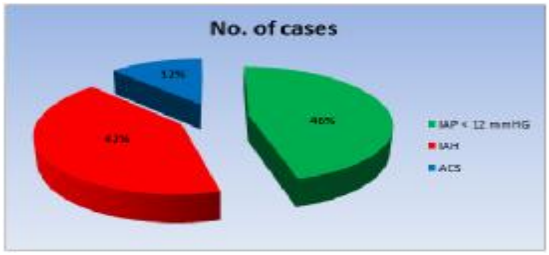
- 22 patients with IAP < 12 mmHg;
- 20 patients with IAH (12 mmHg $\geq$ IAP $\leq$ 20 mmHg);
- 6 patients with ACS (IAP > 20 mmHg);

Table no. 3. The IAP values of AP patients

IAP value	Severity(depending on IAP)	No. of cases
IAP < 12 mmHg	AP with normal IAP	22 (45.83%)
12 mmHg $\leq$ IAP $\leq$ 20mmHg	AP with IAH	20 (41.66%)
IAP > 20 mmHg	AP with ACS	6 (12.5%)

Of f48 patients, 22 (45.83%) had mild forms of IAP < 12 mmHg, 26 (54.16%) patients presented intra-abdominal hypertension (the sustained increase of IAP $\geq$ 12) out of which 6 (12.5%) patients presented abdominal compartment syndrome with IAP> 20 mmHg and organ failure.

Figure no. 2. The division of acute pancreatitis depending on IAP value



26 patients had IAH and ACS. In the patient group with ASP, 22 (88%) patients had IAH or ACS. The 6 patients with ACS were in the ASP group, where they represented 24 % of the cases. In the group of patients with MAP, 4 (17.39%) patients had IAH. 16 patients out of 25 (64%) with SAP had IAH 48 hours after admission.

The patients with intra-abdominal pressure and abdominal compartment syndrome presented SIRS and often MSOF (table no. 1). Mortality in the ACS group was of 83.33% (5 patients) through MSOF and septic shock

A patient developed ACS during the first week of disease. This patient presented ACS (IAP 23 mmHg, renal, respiratory and cardiovascular failure) on the 5th day from admission and he underwent surgery during the first week of disease. The patient died during the third week of hospitalization. The intervention consisted of decompressive laparotomy and double drainage, open abdomen method. 2 of the patients developed ACS during the second week of hospitalization. The first presented ACS (IAP 23 mmHg, respiratory and renal failure, coagulopathy) on the 10th day from admission. He underwent decompressive laparotomy in the second week of disease (laparotomy, cholecystectomy, lavage, peritoneal drainage) and further interventions in the next weeks of disease (laparotomy, sequestrectomy, the evacuation of infected necrosis, lavage, drainage) and died after a long period of hospitalization (97 days). The second patient developed ACS (IAP 21 mmHg, renal and respiratory failure) on the 12th day of hospitalization; he did not undergo any surgery and died on the 14th day of hospitalization due to MSOF.

The other 3 patients with ACS developed intra-abdominal pressure > 20 mmHg in the 3rd and 4th weeks of hospitalization, they underwent one or several surgical interventions, with an unfavourable outcome and death in 2 out of the 3 cases.

As regards the establishment of a correlation between maximum intra-abdominal pressure and maximum serum values of procalcitonin in 48 patients with acute pancreatitis, the data were gathered in the table below. The majority of the patients with IAH had serum levels of PCT between 2 and 10 ng/ml and all of the 6 patients had values of PCT > 10 ng/ml.

Table no. 4. The division of the patients according to the values of procalcitonin

Variables	The presence of the variable IAP max ≥ 12 mmHG (n)	The absence of the variable IAP max< 12mmHg (n)
PCT < 0.5 ng/ml	2	9
PCT : 0.5 - 2 ng/ml	4	10
PCT : 2 – 10 ng/ml	14	3
PCT > 10 ng/ml	6	0

PCT, procalcitonin; IAP inter-abdominal pressure, ; n, number of cases.

Figure no. 3. The division of patients with IAP < 12 mmHg depending on PCT values

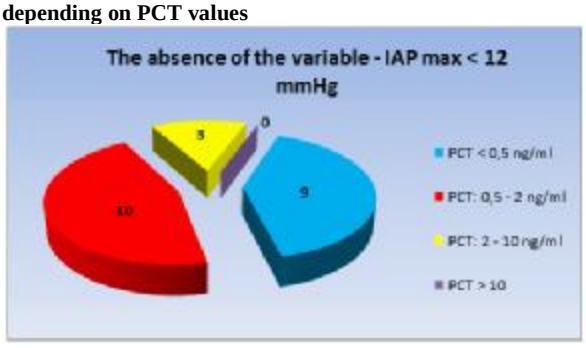


Figure no. 4. The division of the patients with IAP ≥ 12 mmHg, depending on PCT values

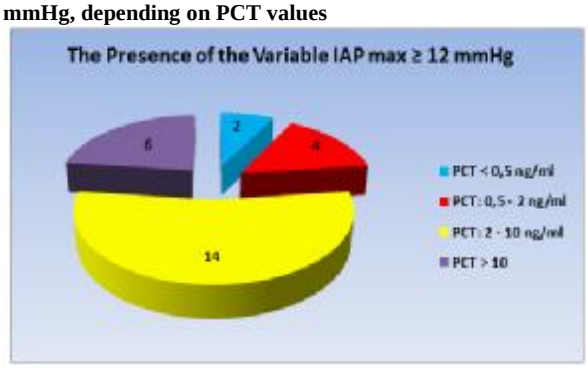
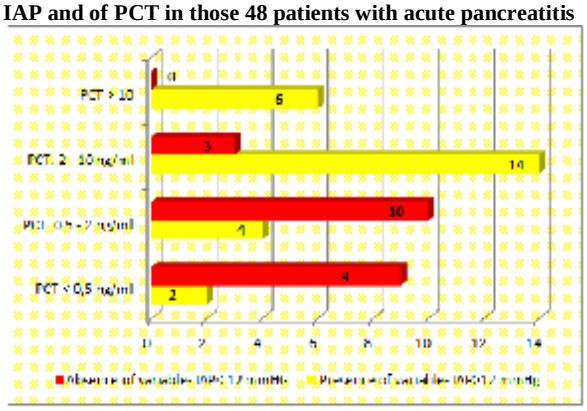
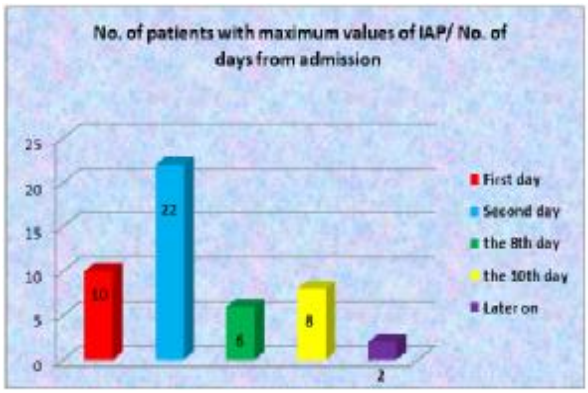


Figure no. 5. Correlation between the maximum values of IAP and of PCT in those 48 patients with acute pancreatitis



Out of 48 patients, the IAP maximum values recorded were the following: on the first day of admission, in 10 patients, on the second day in 22 patients, on the 8th day in 6 patients, on the 10th day in 8 patients and later on in 2 patients. The IAP value 48 hours after admission was significantly higher in ASP patients, and maximum IAP was significantly higher in those with a fatal outcome.

Figure no. 6. Distribution of patients according to the number of hospitalization days where they reached maximum IAP



The PCT maximum levels were registered on the first hospitalization day in 5 patients, on the second day in 13 patients, on the 8th day in 10 patients, on the 10th day in 8 patients and later on, in 12 patients. The PCT maximum values were significantly higher in patients with SAP and the patients who did not survive.

Figure no. 7. Distribution of patients according to the number of hospitalization days where they reached maximum IAP

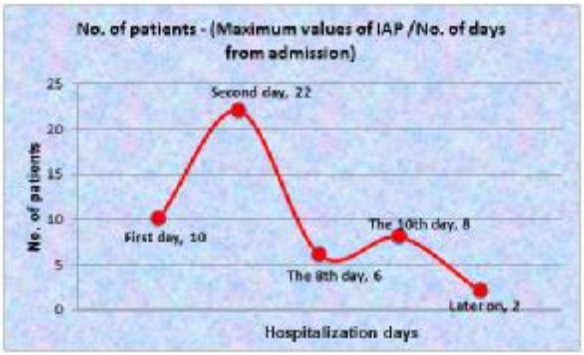


Figure no. 8. Distribution of patients according to the number of hospitalization days when the maximum PCT levels were reached

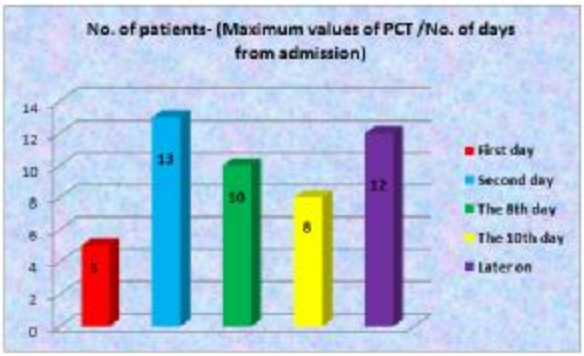
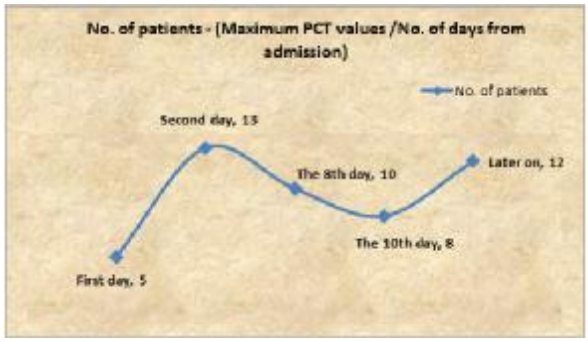


Figure no. 9. Distribution of patients according to the number of hospitalization days when the maximum PCT levels were reached



DISCUSSIONS

In this study we have analysed the correlation between maximum IAP and maximum serum levels of PCT in patients suffering from acute pancreatitis included in this study.

Procalcitonin is used in medical practice for the diagnosis of SAP and for monitoring the outcome of the disease.(1,2,5,7,9) Pancreatic infection and sepsis are major complications in SAP, with a significant impact on the management and the evolution of the disease. More studies, among which that of Bettina M. Rau et al. (11) have proved that patients with SAP who developed infected pancreatic necrosis and MODS, or those who have died, there were found significantly higher concentrations of maximum PCT during the course of the disease, as compared to those where these complications were missing. The serum levels of procalcitonin higher than 3.8 ng/ml have a predictive value for the emergence of organic dysfunction.(2)

A recent study regarding the role of procalcitonin in the identification of patients with acute pancreatitis assigned to this test a sensibility of 72 % and a specificity of 86% (2).

We have also determined in the present study the maximum PCT value reached during the course of disease and we compared it to maximum IAP. There has been a significant correlation of the evolution of both markers, also described by means of the similar curves in representing their evolution referred to hospitalization days. In this study, as in the one performed by Bezmarevic M. et. al. (5), we have observed high PCT values not only in those with ACS, at it is evidenced in other studies. Severe retroperitoneal inflammation combined with aggressive volemic resuscitation in the early stages of AP, may contribute to visceral edema and the increase of IAP. The increase of IAP causes intestinal hyperfusion even at values of 8-12 mmHg (12,13), whereas IAH contributes to the hypoperfusion of the pancreas.(14)

Seriate measurements have shown that the majority of patients reached IAP and PCT maximum values 48 hours after admission. The maximum PCT values had biphasic evolution with an increase of the maximum values on the second day of admission in the majority of patients and later after 10 days from admission, in a great number of patients. A similar evolution is recorded by IAP values in AP patients, the majority reaching maximum values after 48 hours from admission. In the early stages of AP, the increase of IAP and PCT may be caused by the paralytic ileus caused by inflammation and pain.(5,15,16,17)

The belated increase of PCT may be caused by the infection of the pancreatic necrosis, abscess and/ or sepsis.(18,19,20)

The infection of pancreatic necrosis is the most important risk factor for AP mortality and it is typically produced during the second or the third week of disease, in 40-70% of patients with necrotizing pancreatitis. The prevention, the diagnosis and the best treatment of infection in ASP are essential for the evolution of this disease.(2)

As IAP indirectly affects the degree of inflammation in AP patients, it can be a good marker of disease severity. This is also supported by the fact that there is a significant correlation between IAP values and PCT serum values.(5) The early detection of bacterial translocation in the intestines and the identification of the factors which determine the degree of translocation may reduce local and systemic complications in acute pancreatitis.(21,22,23) Antibioprophylaxis and abdominal decompression may reduce the mortality of patients with AP.

We have decided to use the maximum PCT and IAP values out of the following reasons. Firstly, this is due to the fact that maximum IAP values reached by AP patients are closely correlated with the unfavourable outcome of disease, the emergence of severe complications and mortality rate. Secondly, PCT maximum values are associated with severe inflammation, with bacterial translocation, influencing mortality rate in AP. PCT high values were recorded in those with ACS and in the ones with a fatal outcome. IAP maximum values could be correlated with PCT maximum values, the increase of IAP being accompanied by the increase of PCT.

CONCLUSIONS

IAP increase is followed by the elevation of the serum values of PCT. In this study, we have observed PCT high values in IAH patients, not only in those with ACS, as it is shown in other studies. Seriate measurements have shown that the majority of patients reached IAP and IAP maximum values after

48 hours from admission. PCT maximum values have a biphasic evolution, reaching maximum values on the second day of hospitalization in most patients and later, 48 days after admission in a large number of patients. A similar evolution is recorded by IAP values in AP patients. Maximum IAP could be correlated with PCT maximum serum levels. In the early stages of AP, the increase of both IAP and PCT is caused by inflammation, paralytic ileus and pain. The belated PCT increase is caused by the infection of pancreatic necrosis, abscess and/ or sepsis.

Maximum IAP values reached by AP patients are closely correlated with the unfavourable outcome of disease, emergence of severe complications and mortality rate. PCT maximum values are associated with severe inflammation, bacterial translocation, also influencing mortality rate in AP. High PCT values were recorded both in those with ACS and in survivors.

In the majority of patients with acute pancreatitis, PCT and IAP values reached maximum levels in the early stages (48 hours after admission) of the evolution of acute pancreatitis and it may indicate the fatal outcome of the disease.

REFERENCES

1. Lipsett PA. Acute Pancreatitis. Textbook of Critical Care. Fifth Edition, edited by Mitchell P. Fink, Edward Abraham, Jean-Louis Vincent, Patrick M. Kochanek. 2005;122:1021-32.
2. Lipsett PA. Acute Pancreatitis. Textbook of Critical Care. 6th Edition, edited by Mitchell P. Fink, Edward Abraham, Jean-Louis Vincent, Patrick M. Kochanek. 2011;104:785-94.
3. Marino PL. Pancreatitis and liver failure. Marino's The ICU Book fourth edition. 2014;39:719-36.
4. Chen H, Li F, Jia JG. Abdominal compartment syndrome in patients with severe acute pancreatitis in early stage. World J Gastroenterol. 2008;14(22):3541-3548.
5. Bezmarevic M, Mirkovic D, Soldatovic I, Stamenkovic D, Mitrovic N, Perisic N, Marjanovic I, Mickovic S, Karanikolas M. Correlation between procalcitonin and intra-abdominal pressure and their role in prediction of the severity of acute pancreatitis. Pancreatology. 2012;12:337-343.
6. Hidalgo Rosas JM, Navarro Soto S, Serra Araci J, Rebasa Cladera P, Hernandez Borlan R, Vazquez Sanchez A, Bory Ros F, and Grande Posa L. Intra-abdominal pressure as a marker of severity in acute pancreatitis. Original Communications. J Surg. 2007;173-178.
7. Beger HG, Rau B, Mayer J, Pralle U. Natural Course of Acute Pancreatitis, World J Surg. 1997;21(2):130-135.
8. B.R.A.H.M.S – PCT – Q - Rapid diagnosis of septic infections; 2012.
9. Grigoraş I. Pancreatita acută - forma severă. Jurnalul de Chirurgie, Iaşi. 2005;1(1):9-20.
10. Kron IL, Harman K, Nolan SP. The Measurement of Intra-abdominal Pressure as a Criterion for Abdominal Re-exploration. Ann Surg. 1984;199(1):28-30.
11. Rau BM, Kemppainen EA, Gumles AA, Buchler MW, Wegscheider K, Bassi C, Puolakkainen PA, Berger HG. Early Assessment of Pancreatic Infections and Overall Prognosis in Severe Acute Pancreatitis by Procalcitonin (PCT). Ann Surg. 2007;245(5):745-754.
12. Milev B, Mircovic D, Bezmarevic M, Misovic S, Mitrovic M, Jovanovic M, et al. Intra-abdominal hypertension and abdominal compartment syndrome. Vojnosanit Pregl. 2010;67(8):674-80.
13. Schwarte LA, Scheeren TW, Lorenz C, De Bruyne F, Fournell A. Moderate increase in intraabdominal pressure attenuates gastric mucosal oxygen saturation in patients undergoing laparoscopy. Anaesthesiology. 2004;100:1081-7.
14. Caldwell CB, Ricotta JJ. Changes in visceral blood flow with elevated intra-abdominal pressure. J Surg Res. 1987;43:14-20.
15. Maruna P, Frasko R, Gurlich R. Plasma procalcitonin in patients with ileus. Relations to other inflammatory parameters. Physiol Res. 2008;57:481-6.
16. Madl C, Druml C. Systemic consequences of ileus. Best Pract Res Clin Gastroenterol. 2003;17(3):445-56.
17. Grollman AI, Goodman S, Fine A. Localized paralytic ileus: an early roentgen sign in acute pancreatitis. Surg Gynecol Obstet. 1950;91(1):65-70.
18. Al-Nawas B, Krammer I, Shah PM. Procalcitonin in the diagnosis of severe infections. Eur J Med Res. 1996;1:331-3.
19. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaund J, Bohuon C. High serum ocalcitonin concentrations in patients with sepsis and infections. Lancet. 1993;341:515-8.
20. Kylanpaa-Back MI, Takala A, Kemppainen E, Puolakkainen P, Repo H. Procalcitonin strip test in early detection of severe pancreatitis. Br J Surg. 2001;88:222-7.
21. Luiten EJ, Hop WC, Endtz HP, Bruining HA. Prognostic importance of gram – negative intestinal colonization preceding pancreatic infection in severe acute pancreatitis: results of a controlled clinical trial of selective decontamination. Intensive Care Med. 1998;24:438-45.
22. Runkel NS, Moody FG, Smith GS, Rodriguez LF, LaRocco MT, Miller TA. The role of the gut in the development of sepsis in acute pancreatitis. J Surg Res. 1991;51:18-23.
23. Gianotti L, Munda R, Alexander JW. Pancreatitis – induced microbial translocation: a study of the mechanisms. Res Surg. 1992;4:87-91.