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Original paper

PROTEIN C AS DIAGNOSTIC AND PREDICTIVE BIOMARKER OF SEPSIS DURING SEVERE INTRA-ABDOMINAL INFECTIONS

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Summary: Severe intra-abdominal infections (IAI) with sepsis syndrome are still associated with high mortality rate (20 60%). This prospective study refers to diagnostic and prognostic importance of protein C detection during severe abdominal sepsis. We treated surgically 22 patients with severe IAI (mostly diffuse peritonitis with sepsis syndrome) vs. 15 patients with hernia repair (control group). During the study the next parameters were analysed: protein C, AT III, plasminogen, alpha-2 antiplasmin, HMWK, C5a, C5-B9 complements, C1-inhibitor, CRP. All the evaluated parameters were different between the study and control groups, with high statistical significance ($p < 0.001$). The results and multivariate statistical analysis revealed the following parameters as very sensitive and important biological markers of abdominal sepsis: protein C, AT III, HMWK, C5-B9, C1-inhibitor ($p < 0.0001$ 0.026). The clinical difficulties of intra-abdominal sepsis are due to inherent problems of the limited clinical signs and the complexity of the distribution of infection. Inflammatory process is often well under way before the clinical signs and symptoms of sepsis are present. Early diagnosis of plasma proteolytic disturbances is, from the diagnostic and predictive point of view, very important in abdominal sepsis. According to multivariate statistical analysis protein C is the most significant diagnostic marker of sepsis during severe IAI ($p < 0.0001$).

Key words: protein C, biomarker, septic abdomen, sepsis

Introduction

Sepsis is a complex condition necessitating prompt diagnosis and adequate treatment. The total of 18 million cases of sepsis are recorded annually in the world, with 135,000 lethal outcomes in Europe and 215,000 ones in USA (1). Septic syndrome of the abdominal origin accounts for 30 35% of the above mentioned figures (1, 2).

The term sepsis in the abdominal surgery designates presence of the septic abdomen as the major trigger of a range of pathophysiological events. Systemic inflammatory reaction to intra-abdominal septic focus is a highly complex phenomenon which is always directed toward anti-infection defense and homeostasis preservation. In case of intensive bacterial invasion, the systemic response results in excessive production of inflammation mediators, damaged tissue perfusion and multiple organ dysfunction (MODS) (2). Development of septic complications of the intra-abdominal infection (IAI) is rather progressive and rapid, representing immediate threat to patients life, and thus they necessitate rapid diagnosis and timely and adequate therapeutic approach (3). In spite of the modern approach to its treatment, intra-abdominal sepsis is burdened with high incidence and mortality rate (20 50%). Progression of the septic shock is associated with increasing mortality, ranging from 40% to 70% (4, 5).

Septic cascade is initiated by the inflammatory reaction to bacterial pathogens (endotoxin, cell fragments G+ bacteria) (6). The order of subsequent events (inflammatory cascade) is the result of cytokine actions resulting from their binding to receptors. TNF, IL-1 and IL-6 are the most potent pro-inflammatory cytokines enabling activation of polymorphonuclears,

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adhesive processes between leukocytes and endothelial cells, protease release as well as activation of arachidonic and plasmatic cascades (coagulation, fibrinolytic, kalikrein, contact-activation) (7). Simultaneously, regulatory anti-inflammatory cytokines, such as IL-4 and IL-10 tend to accomplish negative feed-back mechanism related to inflammatory and coagulation reactions. These anti-inflammatory cytokines are mediators of the compensatory antiinflammatory response syndrome (CARS) that induces inhibition of TNF, IL-6, T-lymphocytes and macrophages, enhancing production of the acute phase proteins and immunoglobulins (8). As a result of imbalance between SIRS and CARS strengths, homeostatic disorders lead to different clinical sequels. Excessive response of the systemic inflammatory response syndrome (SIRS) results in septic shock and/or disseminated intravascular coagulation. Predominant presence of CARS mediators may lead to suppression of the immune system, which also has negative consequences in presence of infection (9).

Protein C system plays a crucial role in control of microvascular coagulation and inflammation. It is one of the basic regulatory systems of homeostasis expressing potent anticoagulant, pro-fibrinolytic and anti-inflammatory properties (10). It is highly important in pathophysiology of sepsis. Protein C inactive precursor, and activated protein C (APC), K-vitamin dependent-serine protease with potent biological properties have central place within the system. Protein C is converted into APC under the influence of thrombin complexes with thrombomodulin on the endothelial protein C receptors (EPCR) in presence of protein S. Normal levels of the circulating protein C range from 2800 to 5600 ng/mL (80% 140%) with 10 hour half-life, as opposed to APC whose half-life is only 20 minutes, and normal circulating levels range within 1 3 ng/mL (7, 8, 10, 11). Close correlation between intra-abdominal infection and sepsis necessitates highly precise, fast and complex diagnostic and therapeutic approaches. Therapeutic improvements were achieved over the latest several years owing to partially modified and more aggressive surgical approach, as well as owing to modern antibiotics, however for several recent years, the improvements have been made only in the field of knowledge on the pathophysiology of sepsis. The most recent development based on understanding of complex inter-reactions among coagulation, inflammatory and fibrinolytic cascades has led to accelerated development of new therapeutic approaches and strategies. In 2000, a large step forward was made in fight against septic syndrome. Several completed clinical trials evidenced a significant improvement in treatment of sepsis owing to application of the recombinant human activated protein C (rhAPC) (10 13).

Generalized plasmatic proteolysis, developing as a result of imbalance of active serine proteases and functional inhibitory systems, represents one of the basic pathophysiological disorders accompanying abdominal sepsis. Septic cascade, i.e. its inflammatory and coagulation components in severe intra-abdominal infections are initiated before clinical manifestations (febricity, tachycardia, tachypnea, hypotension) which indicates the significance of determination of early biological markers of sepsis. Therefore, the aim of the study was to analyse plasmatic cascade disturbances during the severe IAI with sepsis syndrome, and determination the biochemical markers of sepsis.

Material and Methods

Research methodology is based on a prospective study comprising 37 patients classified into the following groups, based on their underlying condition: *Study group:* 22 surgically treated patients due to severe intra-abdominal infection (IAI) with accompanying sepsis. *Control group:* 15 surgically treated (hernia repair) patients free of any signs of the infection syndrome.

The blood samples for determination of the analyzed parameters were obtained preoperatively, as well as on the postoperative days one, two, three, five, seven and ten.

Protein C is determined by use of automated BCT Analyzer (Behring Coagulation Timer) and Berichrom Protein C reagents manufactured by DADE Behring, Marburg GmbH. The complex functional analysis is based on conversion of protein C into activated protein C (APC) (using snake venom proteases), followed by measurement of its activity, indirectly through aPTT. Neothromtin and $CaCl_2$ are used for activation of the internal coagulation pathway. Functional activity of activated protein C (APC) is determined according to kinetic test, measuring absorption rise to 405 nm. The values are expressed as percentages, normally ranging from 80 to 140% (14, 15).

In addition to protein C, the following parameters of the plasmatic cascades (coagulation, fibrinolytic, kalikrein-kinin) were monitored and analysed: antithrombin III, plasminogen, alpha-2 antiplasmin, HMWK, C1-inhibitor. They were determined using turbidimetric methodology (Behring Hromo Timer) and Berichrom diagnostic kits (DADE Behring, Marburg GmbH). The values represent functional activity, and are expressed in percentages (16, 17). C5a and C5-B9 components of system complements were measured by ELISA assay using DADE Behring reagents, and the values are expressed in mg/L (18).

Statistical analysis

The results are presented as mean values with dispersion measures (SD, CV). Statistical analysis was performed using: Fisher's t-test, regression model testing (Yc), Pearson's correlation coefficient (r), Determination coefficient (R2), Multivariate analysis (multiple and partial correlation coefficient) (19, 20).

Results

Etiology of intra-abdominal infections (IAI) significantly influences treatment outcome. Spontaneous diffuse peritonitis is the most predominant (68%), followed by a group of postoperative peritonitis (27.5%) burdened with a high mortality rate (50%). Average value of APACHE II score in IAI group was 17 points. The actual mortality rate (23%) was lower than the predicted one (37%).

As for the group treated for abdominal sepsis, preoperative values were normal in 45% of the patients, while more severe protein C activity disorders (below 60%) were evidenced in 18%. Average protein C activity in abdominal sepsis indicates significant differences recorded on the preoperative day between the survived and deceased patients ($p < 0.037$). Trends and differences in the average postoperative protein C activity between the survived and deceased patients *(Table I)* indicate crucial significance of the postoperative day two, with divergence of values related to more prominent normalization, increased activity in the group of survivors and further decrease of the activity in the group of the deceased. Difference in average postoperative protein C values is confirmed as statistically highly significant on the postoperative days seven ($p < 0.032$) and ten ($p < 0.021$). Regression model testing shows activity trend and high correlation between duration of illnes and severity of the abdominal septic syndrome, protein C activity changes related to decrease of its value and degree of activation of the coagulation and inflammatory cascade (r-0.80; $p < 0.01$). As for the control group, protein C activity is permanently maintained within normal range *(Table I)* which eliminates the influence of the surgical intervention itself on more considerable changes in protein C activity and coagulation cascade. Difference in protein C activity between the control and study groups during the whole studied period is highly statistically significant ($p<0.005$; $p<0.001$; $p<0.033$). Multivariate statistical analysis of the plasmatic parameters confirms statistically highly significantly (multiple correlation coefficient r-0.761; $p<0.0001$) the importance of the decreased protein C activity in correlation with activation of the inflammatory and coagulation cascade in abdominal sepsis.

Antithrombin III, plasminogen, alpha 2-antiplasmin, HMWK, C1-inhibitor, C5a and C5-B9 components of complement system paralelly analysed parameters show the activation and disturbances of all the proteolytic cascade systems (coagulation, fibrinolytic, kalikrein-kinin and system of complements) during severe intra-abdominal infections (IAI) associated with the sepsis syndrome *(Table II)*. All the evaluated para-

Table I Protein C activity (%) in abdominal sepsis and control group

Abdominal sepsis group	Outcome	Minimal	Maximal	Mean value	SD	CV (%)	Statistics
preoperative	live	47	119	81.08	21.57	26.60	t=2.293
	died	41	73	57.20	12.50	21.85	p<0.037
	total	41	119	74.06	22.02	29.73	---
1st postoperative day	live	45	104	75.82	15.78	20.81	t=1.756
	died	50	83	62.20	12.91	20.76	p>0.05
	total	45	104	72.73	15.99	21.98	---
2nd postoperative day	live	49	121	75.00	20.02	26.69	t=1.967
	died	51	84	65.60	16.43	25.04	p>0.05
	total	49	121	72.86	19.31	26.50	---
3rd postoperative day	live	34	121	83.44	24.16	28.95	t=1.771
	died	52	89	63.00	14.88	23.62	p>0.05
	total	34	121	78.57	23.70	30.16	---
5th postoperative day	live	23	129	83.24	24.63	29.60	t=1.182
	died	53	96	69.20	17.20	24.85	p>0.05
	total	23	129	80.05	23.56	29.43	---
7th postoperative day	live	59	101	81.10	15.65	19.30	t=2.484
	died	51	54	52.50	2.12	4.04	p<0.032
	total	51	101	76.33	18.02	23.61	---
10th postoperative day	live	79	108	95.50	14.34	15.02	t=3.666
	died	55	57	56.00	1.41	2.53	p<0.021
	total	55	108	82.33	23.24		
Control group		Minimal	Maximal	Mean value	SD	CV (%)	
preoperative		82	104	92.50	6.47	6.99	
1st postoperative day		82	107	93.64	7.72	8.25	
3rd postoperative day		80	105	93.07	6.72	7.22	

Table II Plasmatic parameters in abdominal sepsis

Parameter	Out come	preoperative	1st p.o. day	2nd p.o. day	3rd p.o. day	5th p.o. day	7th p.o. day	10th p.o. day
Antithrombin III (%)	live	77.75	81.41	78.76	82.44	86.88	88.20	95.75
	died	61.20	78.00	69.80	68.60	68.80	82.50	87.00
	total	72.88	81.41	76.73	79.14	82.77	87.25	92.83
Plasminogen (%)	live	91.58	90.88	86.29	91.69	96.53	95.70	99.25
	died	70.60*	71.20*	81.00*	65.00*	63.60*	53.50*	66.00*
	total	85.41	86.41	85.09	85.33	89.05	88.67	88.17
α_2-antiplasmin (%)	live	96.83	101.76	90.88	96.13	92.12	88.70	101.80
	died	83.40	91.00	78.60	68.20	66.80*	67.00	62.00*
	total	92.88	99.32	80.36	84.24	80.91	76.75	86.14
HMWK (%)	live	74.82	71.12	72.94	85.31	80.55	82.80	88.25
	died	65.20	47.68	65.20	57.60	39.60*	50.00	49.50
	total	72.64	65.79	71.18	78.71	67.75	77.33	75.33
C5-a (mg/L)	live	3.78	3.11	2.71	2.49	2.20	2.50	2.55
	died	2.32	2.59	2.12	2.06	3.89	2.69	4.05
	total	3.37	2.99	2.57	2.39	2.58	2.53	3.15
C5-B9 (mg/L)	live	1469	1237	1193	1041	1021	1023	1157
	died	1299	1424	1176	1374	2111*	860	2730*
	total	1419	1280	1189	1120	1269	993	1786
C1-inhibitor (%)	live	131.62	133.06	133.47	139.58	129.69	135.50	148.33
	died	112.80	120.00	118.00	109.40*	108.40*	107.00*	107.50
	total	126.39	130.09	129.95	132.38	124.62	130.75	132.00
CRP (IU)	live	171.96	221.62	175.56	153.98	149.07	163.29	188.67
	died	241.40	245.40	190.00	174.68	158.82	160.00	123.15
	total	192.38	227.02	178.84	158.90	151.28	162.69	162.46

* Statistically significant difference (Fisher's t-test $p < 0.01$) when comparing survived and died patients

Table III Plasmatic Score System (PSS)

PARAMETER	POINTS				
	0	1	2	3	4
Protein C (%)	80 140	70 80	60 70	50 60	< 50
Antithrombin III (%)	80 120	70 80	50 70	< 50	
Plasminogen (%)	75 140	60 75	50 60	< 50	
α_2-antiplasmin (%)	80 120	60 80	< 60		
HMWK (%)	75 130	60 75	40 60	< 40	
C5-a (mg/L)	0.15 0.50	0.50 2.00	2.00 3.00	> 3.00	
C5-B9 (mg/L)	200 400	400 1000	1000 1500	1500 2000	> 2000
C1 inhibitor (%)	80 125	125 150	150 200	< 80 > 200	
CRP (IU)	< 5	5 100	> 100		

Assessment of severity and prognosis of the abdominal septic syndrome
TOTAL SCORE: 0 9 points Slight disturbance degree (Good prognosis)
10 19 points Moderate disturbance degree (Moderate prognosis)
20 27 points Severe disturbance degree (Critical prognosis)

meters were different between the survived patients and the patients with lethal outcome, as well as between study and control groups, with high significance ($p < 0.001$). In order to incorporate the concept of generalized plasmatic proteolytic activation in the evaluation of patients with abdominal sepsis, Plasmatic Score System (PSS) *(Table III)* is established for the purpose of assessment of severity and prognosis of the abdominal septic syndrome. The PSS is defined as the sum of the points, according to deviations from the normal plasma pool values for nine parameters (protein C, AT III, plasminogen, α_2-antiplasmin, HMWK, C1-inhibitor, C5a, C5-B9 and CRP) measured for the PSS calculation.

Discussion

Intra-abdominal infections are still an exceptionally severe problem in everyday surgical practice. In spite of modern therapeutic approaches, intra-abdominal sepsis is still burdened with relatively high incidence and mortality rates (20 60%) (3 5).

In the course of IAI, peritoneal cavity represents the initial barrier against bacterial infection. Activated macrophages that initiates activation of numerous plasmatic and cell systems makes the second level of defense. Systemic inflammatory response develops under the influence of numerous inflammatory reaction mediators. Excessive activity of the induced mediators leads to numerous damages of the organism and thus, septic syndrome is justifiably also termed »the mediator disease« (21). Activation of the plasmatic systems (coagulation and fibrinolytic cascades, system of complements, kinin-kalikrein system and contact cascade) results in production of acute plasma proteins. Simultaneously, inhibited plasmatic systems (serpines) are attempting to neutralize activation of serine proteases (22).

The fact that basic events encountered in sepsis take place on the cellular level has drawn the attention toward diagnosis of early and discrete plasmatic disorders, and accordingly modern treatment strategies are directed toward blockade of the sepsis mediators. Numerous research attempts within the basic and clinical disciplines have been made aimed at contributing to better understanding of the abdominal sepsis and improvement of therapeutic results.

Activated protein C (APC) represents an active form of the protein C protein S Thrombomodulin pathway and it is one of the most important control inhibitory mechanisms of coagulation. APC inactivates coagulation factors Va and VIIIa, neutralizes the effects of plasminogen activator inhibitor (PAI-1) (23). In addition to anti-thrombotic and profibrinolytic properties, APC also has a direct anti-inflammatory activity that reduces cytokine production (TNF, MIF) and inhibits adhesion of leukocytes to the blood vessel endothelium (22, 23). It expresses indirect anti-inflammatory properties through inhibition of thrombin production. Owing to all the above-mentioned mechanisms APC significantly reduces the processes of microvascular thrombosis and endothelial dysfunction (24). APC blocks Ca pump leading to CD-14 monocyte disorders upon endotoxin response to stimulation (25). APC binds to protein C mononuclear receptors, blocking TNF production (26). Identical endothelial effect was evidenced (25).

Prominent reduction of protein C activity accompanies severe DIC and severe forms of the septic syndrome (21). Protein C level is disturbed, i.e., its activity is reduced at least 18 hours prior to clinical diagnosis of sepsis (27). Protein C activity is reduced in all septic events regardless of their mechanism. Level of the circulating protein C and protein S is reduced due to increased consumption. Circulating cytokines reduce the activity of thrombomodulin and EPCR in the endothelium, which results in reduced protein C activation (10). Neutrophilic elastase decomposes thrombomodulin, leading to system disorders characterized by reduced activation and production. Inhibitory activity in increases in presence of inflammatory processes resulting from increase of alpha-1 antitrypsin and increased value of acute phase protein C4b which binds and blocks protein S, contributing to reduction of protein C activity (13).

The study was conducted within an attempt to examine the role and significance of activation of plasmatic cascades in our settings characterized by diverse pathology of severe, advanced and neglected intra-abdominal infections, and thus to contribute, at least to moderate extent, to diagnosis and prognosis of the diseases rather frequent in our population.

Average preoperative protein C values among the survived and deceased patients treated for intra-abdominal infections and accompanying sepsis were significantly different ($p<0.037$). Postoperative activity was changed and characterized by decreased values in the whole IAI group. Postoperative day two was critical with respect to dissociation of the average protein C values evidenced in the survived and deceased patients, while statistically significant difference was confirmed on postoperative days seven ($p<0.032$) and ten ($p<0.021$). Regression model testing indicates significance of correlation between fall of protein C activity and activation of the coagulation and inflammatory cascade during abdominal sepsis (r-0.80; $p<0.01$). As for the control group, protein C activity is permanently maintained within the normal range, which eliminates the influence of the surgical intervention itself on more significant changes of protein C activity and coagulation cascade. Difference in average protein C value between the study and control groups has remained highly statistically significant over the whole studied period ($p<0.005$; $p<0.001$; $p<0.033$). Multivariate analysis confirms with high statistical significance (multiple correlation coefficient r-0.761; $p<0.0001$) fall of the value and reduction of protein C activity in severe IAI and abdominal sepsis. Accordingly it may be concluded that protein C represents an important biological marker in early diagnosis of coagulation disorders and inflammatory cascade in sepsis.

The newest multicenter clinical study of the third phase (PROWESS) related to application of recombinant human activated protein C (rhAPC-drotecogin alpha) in treatment of sepsis give more than encouraging results. The study was conducted in 164 institutions (11 states) and included total of 1690 patients diagnosed with sepsis. All the above confirms potent anticoagulation and anti-inflammatory APC effects. Finally, the most important effect of APC application is

statistically significant reduction of 28-day mortality in severe sepsis from 30.8% to 24.7% (10 13).

As for the surgical treatment of IAI, the question of early diagnosis of the abdominal septic syndrome is still opened. Defining of early biological markers of the abdominal sepsis is important for establishment of indications for early re-laparatomy. Clinical onset of organic lesions and MODS is accompanied by delayed re-intervention (28 30).

Excessive pathological activation of the plasmatic cascades undoubtedly plays an essential role in pathophysiological events in sepsis. Plasma characterized by prominent imbalance between active serine proteases and their functional inhibitors when numerous potent products and mediators are released, is designated as »pathological perfusate« (22). In the course of extreme and excessive activation of the plasmatic proteolytic cascades, capacity of the regulatory inhibitory systems is exceeded, and the resulting imbalance leads to a range of disorders inducing multiple organ dysfunctions. Association between coagulation, fibrinolytic, kalikrein-kinin cascades and complement system explains potent generalized proteolysis that is activated via endotoxins, damaged endothelium and potent cytokines. The system of contact activation plays a major role in mutual activation of the abovementioned systems.

Based on the analysis of the plasmatic changes accompanying sepsis of the abdominal origin we have attempted to contribute to early and exact biochemical diagnosis of sepsis, as well as to establish new parameters for assessment of severity and prognosis of infection syndrome. Analysis of the obtained results clearly indicates early activation of all plasmatic cascades recorded according to prominent activity changes of the all analysed parameters in the study group. At the same time, except for preoperative changes of CRP values, pathological plasmatic activity was not recorded in the control group ($p<0.001$). Mutual relations between the analyzed parameters as well as different plasmatic systems have been confirmed by multivariate analysis of the obtained results, and clearly confirm either direct or indirect correlation of the analyzed parameters of different degrees. Due to its unspecific character, CRP has not been included in multivariate analysis, however it is scored and included in the calculated Plasmatic Score System (PSS) *(Table III)* aimed at assessment of severity and prognosis of the infection syndrome.

From the diagnostic point of view, the interval between laboratory detection of the plasmatic disorders and their complete clinical manifestation is of the utmost importance (31). With this respect, we have tried to determine degree of sensitivity of each analysed parameter having in mind the significance of early biochemical diagnosis of plasmatic disorders in abdominal sepsis. Multivariate analysis (multiple correlation coefficient) included all the analyzed parameters of the plasmatic cascades and it was determined that reduction of protein C activity showed statistically highly significant importance (multiple correlation coefficient r-0.761; $p<0.0001$) in early diagnostic detection of activation of coagulation and inflammatory cascades in sepsis. From predictive point of view, the low protein C activity is associated with poor outcome.

DIJAGNOSTIČKI I PROGNOSTIČKI ZNAČAJ PROTEINA C KAO BIOMARKERA SEPSE U TEŠKIM INTRA-ABDOMINALNIM INFEKCIJAMA

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Kratak sadržaj: Teške intra-abdominalne infekcije (IAI) sa septičnim sindromom opterećene su visokom stopom mortaliteta (20 60%). Ova prospektivna studija analizira dijagnostički i prognostički značaj određivanja proteina C u abdominalnoj sepsi. Podaci se odnose na grupu pacijenata (22) sa teškom IAI i pratećim septičnim sindromom (studijska grupa) i grupu pacijenata (15) lečenih hirurški zbog preponske hernije (kontrolna grupa). Osim proteina C, određivani su sledeći plazmatski parametri: AT III, plazminogen, alfa-2 antiplazmin, HMWK, C5a, C5-B9 komponente sistema komplementa, C1 inhibitor, CRP. Koeficijent višestruke korelacije ukazuje na statističku značajnost ($p<0.0001$ 0,026) sledećih parametara u dijagnostici plazmatskih poremećaja u sepsi: protein C, AT III, HMWK, C5-B9, C1-inhibitor. Kliničke poteškoće u tretmanu abdominalne sepse odnose se na ograničene kliničke znake i sistemsku propagaciju sa druge strane, koja se odvija znatno pre ispoljavanja kliničke simptomatologije. Otuda proističe značaj bioloških markera sepse, prvenstveno u dijagnostičkom, ali i u prognostičkom smislu. Prema rezultatima studije protein C upravo poseduje pomenuta svojstva, potvrđena multivarijantnom statističkom analizom ($p<0.0001$).

Ključne reči: protein C, biomarker, septični abdomen, sepsa

References

1. Angus DC, Linde-Zwirble WT, Lidicker J. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med 2001; 29: 1303 10.
2. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS), multiple organ dysfynction syndrome (MODS), multiple organ failure (MOF): are we winning battle? Shock 1998; 10: 79 89.
3. Wittmann DH, Aprahamian C, Bergstein JM, Wallace JR. STAR and STIR effectively treat abdominal compartment syndrome and reduce mortality of traumatic and infectious abdominal catastrophes. J Int Care Med 2000: 15: 201 20.
4. Farthmann EH., Schoffel U. Principles and limitations of operative management of intrabdominal infections. World J Surg 1990; 14: 210 17.
5. Garcia-Sabrido JM, Talado JM, Christou NV. Tretment of severe intaabdominal sepsis and /or necrotic foci by an open abdomen approach: Zipper and zipper-mesh techniques. Arch Surg 1988; 123: 152 6.
6. Berger D. The role of endotoxin in peritonitis. Dig Surg 1996; 13: 384 9.
7. Carvalho AC, Freeman NJ. How coagulation defects alter outcome in sepsis. J Crit Illness 1994; 9: 51 75.
8. Boldt J. Changes of the hemostatic network in the critically ill. In: Vincent JL. ed. Yearbook of Intensive care and Emergency Medicine. Berlin: Springer, 2001: 287 5.
9. Schein M, Wittman DH, Holzheimer R, Condon RE. Hypothesis: Compartmentalizacion of cytokines in intraabdominal infection. Surgery 1996; 11: 694 700.
10. Bernard GR, Hartmann DL, Helterbrand JD, Fisher CJ. Recombinant human activated protein C (rhAPC) produces a trend toward improvement in morbidity and 28-day survival in patients with severe sepsis. Crit Care Med 1999; 27 (2 Suppl): S33 S35.
11. Bernard GR. Late-breaking clinical trial results: multicenter, randomized, placebo-controlled trial of recombinant human activated protein C in sepsis. Program and abstracts of the 30th International Educational and Scientific Symposium of the Society of Critical Care Medicine: 2001 Feb 10 14; San Francisco, USA. Available online at www.medscape.com/medscape/cno/2001/SCCM.
12. Shaw A. Potential Breaktrough in the fight against severe sepsis: The PROWESS trial. Program and abstracts of the 30th International Educational and Scientific Symposium of the Society of Critical Care Medicine: 2001 Feb 10 14; San Franicisco, USA. Available online at www.medscape.com/medscape/cno/2001/SCCM
13. Bernard GR, Vincent JL, Laterre PF. Efficiacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344: 699 709.
14. Yan SB, Dhainaut JF. Activated protein C versus protein C in severe sepsis. Crit Care Med 2001; 29 (7 Suppl): S69 S74.
15. Dhainaut JF, Yan SB, Cariou A, Mira JP. Soluble thrombomodulin, plasma-derived unactivated protein C, and recombinant human activated protein C in sepsis. Crit Care Med 2002; 30 (5 Suppl): S318 S323.
16. Lamle B, Tran TH, Ritz R, Duckert F. Plasma prekalikrein, FXII, antithrombin III, C1-inhibitor in critically ill patients with suspected disseminated intravascular coagulation. Am J Clin Pathol 1984; 82: 396 404.
17. Aasen AO. The proenzyme functional inhibition index. A new parameter for evaluation of the severely injured and septic patients. Acta Chir Scand 1985; 522: 211 33.
18. Hsueh W, Sun X, Rioja LN, Gonzales-Crussi F. The role of the complement system in shock and tissue injury induced by TNF and endotoxin. Immunology 1990; 70: 309 14.
19. Neter J, Kutner M, Machtshein C, Wasserman W. Applied linear statistical models. 4th ed. Chicago, Sydney, Toronto: Irwin, 1996: 560.
20. Daniel W. Biostatistics. 7th ed. New York: John Winey & Sons Inc., 1999: 840.
21. Hesselvik JF, Malm J, Dahlback BF. Protein C, protein S and C4b binding protein in severe infection and septic shock. Thromb Haemost 1991; 65: 126 9.
22. Aasen AO. The role of proteolytic enzyme systems with particular emphasis on the plasma kalikrein-kinin system during septicemia and septic shock. In: Vincent JL, Thijs LG. eds. Septic Shock. Berlin: Springer Verlag, 1990: 116 28.
23. Marlar RA, Endres BJ, Miler C. Serial studies of protein C and its plasma inhibitor in patients with DIC. Blood 1985; 66: 59 63.
24. De Jonge E, Levi M, Van der Poll T. Natural anticoagulants in disseminated intravascular coagulation and sepsis. In: Vincent JL. ed. Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer, 2001: 348 52.
25. Hartmann DL, Bernard GR. Protein C activity by baseline predicts the development of shock and 28 day mortality in patients with severe sepsis. Intensive Care Med 1998; 24 (1 Suppl): S138 S138.
26. Fourrier F, Chopin C, Goudemand J. Septic shock, multiple organ failure and disseminated intravascular coagulation. Compared patterns of AT III, protein C and protein S deficiences. Chest 1992; 101: 816 823.
27. Greg SM. The complex role of coagulation in the pathophysiology of sepsis. Program and abstracts of the 30th International Educational and Scientific Symposium of the Society of Critical Care Medicine: 2001 Feb 10 14; San Francisco, USA. Available online at www.medscape.com/ medscape/cno/2001/SCCM.

28. Teichman W, Herbig B. Scheduled Reoperations for Diffuse Peritonitis. Dig Surg 1996; 13: 396 399.

29. Wittman DH, Schein M, Condon RE. Management of secondary peritonitis. Ann Surg 1996; 224: 10 8.

30. Wittmann DH. Operative and nonoperative therapy of intra-abdominal infections. Infection 1998; 26: 335 51.

31. Macias W, Derchak PA. Coagulopathy may occur before the clinical diagnosis of organ dysfunction. Crit Care Med 2003; 31 (1 Suppl): S100 S110.

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