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Хірургічне лікування хворих з абдомінальним сепсисом з урахуванням прогнозу виконання повторних операцій

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Surgical treatment of patients with abdominal sepsis taking into account the prediction of the implementation of re–operations

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Реферат

Мета. Покращення результатів хірургічного лікування пацієнтів з абдомінальним сепсисом шляхом індивідуалізації терапевтичної тактики з урахуванням вірогідності післяопераційних ускладнень та прогнозування результатів лікування.
Матеріали і методи. Проаналізовано результати лікування дорослих пацієнтів з абдомінальним сепсисом у 2009 та 2019 рр., за винятком гострого холециститу. Пацієнтів розподілили ретроспективно та проспективно відповідно до класифікації Сепсис–3. Було 130 хворих з перитонеальним, 33 – з кишковим, 38 – з панкреатогенним абдомінальним сепсисом. Оцінку результатів порівнювали з використанням сучасних систем: APACHE–II, MPI, MODS та SOFA. Показники оцінювали на 1–шу, 2–гу, 3–тю та 4–ту добу після операції до наступних наслідків первинного операційного втручання.
Результати. Системи прогнозування з площею під ROC–кривою (AUC) > 0,8 включали лише MPI для визначення показань до повторної операції: значення ROC–кривих для 1–ї групи (закрите лікування) становило 0,73, для 2–ї (повторні операції за показаннями) – 0,91, для 3–ї – 0,84 (запрограмовані повторні операції). Однак у 1 групі пацієнтів цей показник становив 0,73, що вказує на те, що він є обмеженим, щоб його застосовувати для прийняття рішення про ефективність повторних операцій у пацієнтів без клінічних ознак септичного шоку.
Висновки. Розрахунок ймовірності виникнення у пацієнта післяопераційного ускладнення та ймовірності смерті залежно від початкової тяжкості стану пацієнта дозволяє вибрати найбільш відповідну тактику хірургічного лікування. У пацієнтів з абдомінальним сепсисом та септичним шоком для зменшення частоти післяопераційних ускладнень та смертності найбільш прийнятним є тактичний підхід із виконанням повторних операцій за показаннями для контролю джерела інфекції, якщо це можливо.

Ключові слова: абдомінальний сепсис; стратифікація ризику; оцінки тяжкості; дослідження; хірургія.

Abstract

Objective. The investigation objective was improvement of the surgical treatment results in patients, suffering abdominal sepsis, using individualized tactics of treatment, taking into account a possibility for the postoperative complications occurrence and the treatment results prognostication.
Materials and methods. The results of treatment of the adult patients, suffering abdominal sepsis in 2009 – 2019 yrs, excluding an acute cholecystitis cases, were analyzed. The patients were divided retrospectively and prospectively in accordance to the Sepsis–3 classification. Of them 130 have suffered peritoneal sepsis, 33 – intestinal one, and 38 – pancreatogenic abdominal. The results estimation was compared with application of modern systems: APACHE–II, Mannheim index of peritonitis (MPI), MODS and SOFA. The indices were estimated on the 1st, 2nd, 3rd and 4th postoperative days before subsequent outcomes of a primary operation.
Results. The prognosis systems with a square under the ROC–curve (AUC) > 0.8 have included MPI only for determination of indications for reoperations: the ROC–curves value for the first subgroup (the closed treatment) have constituted 0.73, for the second subgroup (reoperations in accordance to indications) – 0.91, and for the third – 0.84 (the programmed reoperations). But in the patients of first subgroup this index have constituted 0,73, indicating its application restricting the decision making process, concerning the reoperations efficacy in patients with absence of the septic shock signs.
Conclusion. Calculations of the occurrence possibility for postoperative complications and mortality in patients, depending on their preoperative state severity permits to select a most rational tactics of treatment. Most optimal approach for the rate reduction of postoperative complications occurrence and mortality in patients with abdominal sepsis and septic shock is performance of reoperations in accordance to indications to control the infection source, if it is possible.

Keywords: abdominal sepsis, stratification of risk, estimation of severity, investigations, surgery.

Introduction

Despite successes in the diagnosis and treatment of sepsis, it remains one of the main problems of modern medicine, as it's the main cause of mortality among patients in intensive care units throughout the world [1]. The number of deaths from sepsis is in the same range as myocardial infarction [2]. In the United States the hospitalization rate for patients with sepsis or septicemia increased by 70% from 221 (in 2001) to 377 (in 2008) per 100,000 person–years, and the incidence of serious postoperative sepsis tripled from 0.3% to 0.9 %. Sepsis is particularly common in the elderly and is likely to increase significantly with the age of the population [3, 4]. Sepsis has been called a hidden disaster for public health, with over $ 20 billion in treatment for sepsis which was 5.2% of the total hospitalization costs in the United States in 2011 [4]. Patients who survived sepsis don't have a recognized risk of physical and cognitive impairment and suffer more than double the risk of dying in the next 5 years compared to hospitalized control [5, 6]. So, according to the Centers for Disease Control and Prevention in 2008 alone $ 14.6 billion was spent on hospitalization of sepsis in the United States and from 1997 to 2008 inflation–adjusted cumulative expenditures for the treatment, of patients hospitalized for this disease increased by an average of 11,9% annually [7].

At the Congress of Experts of the European Community of Intensive Care (European Society of Intensive Care Medicine) and the Society of Critical Care Medicine (Society of Critical Care Medicine) it was decided to review the concept of sepsis. Under the auspices of ESICM and SCCM a working group of 19 scientists was formed that included experts in pathophysiology of sepsis, clinical research, infectious pathology, surgery, pulmonology and epidemiology. The working group included authoritative specialists with experience in practical work in this field, original own work as well as participating in international epidemiological and clinical studies to evaluate the effectiveness of medicines. Following the principle of consensus each of the five Associations proposed its co–chair which included S. S. Deutschman (SCCM) and M. Singer (ESICM). From January 2014 to January 2015 four on–site meetings of the working group were held to discuss the existing key provisions for sepsis in the light of new data on immunology, pathophysiology and current clinical practice were formulated criteria for sepsis and septic shock. Subsequently, the proposals of the working group were sent for wider consideration in the 31 major international medical community resulting in the final version of the document published as three separate articles on February 23, 2016 in the journal "JAMA" which has one of the widest audiences of diverse professionals among the world's medical editions [8–10]. The new document was named "Third International Consensus on Sepsis and Septic shock (Sepsis–3)".

Data available in the available literature on the diagnosis, choice of surgical tactics, efficacy of stage laparoscopic or laparotomic means of controlling the source of infection are conflicting. In 2016, the WSES Consensus agreed that planned relaparotomy is not recommended as a general strategy in patients with secondary peritonitis (recommendation 1A). Timely laparotomy is the only surgical option that provides a much better treatment outcome. In such cases, one operation may not be sufficient to control the source of infection in some patients [11]. But current researchers are still debating which therapeutic approach and in what cases best suits surgical strategies for patients with abdominal sepsis (AS). This is facilitated by the fact that, despite the elucidation of mechanisms for the development of postoperative complications, mortality in the development of multiple organ dysfunction (MODS) remains at a very high level and can reach 80%.

The aim of the study was to improve the results of surgical treatment of patients with abdominal sepsis by individualizing therapeutic tactics, taking into account the likelihood of postoperative complications and predicting the outcome of treatment.

Materials and methods

These studies were conducted in 201 patients aged 18 to 70 years for AS, including 61% for men, 39% for women who underwent surgical interventions for the development of AS and were treated at surgical departments of the Municipal Health Care Institution Regional Clinical Hospital – Emergency and Disaster Medicine Center, Kharkiv, Ukraine. All patients were divided into two groups: the first group was a comparison group (84 patients), who had been on treatment from January 2009 to April 2014, and in whom a treatment analysis was retrospectively conducted; the second – the main (117 patients), who were treated from May 2014 to December 2019, and who prospectively studied the effectiveness of the proposed surgical approach, the basis of which was a revised approach to the implementation of surgery of the abdominal cavity, and the vector of treatment was displaced in favor of performing relaparotomy/relaparoscopy on–demand patient's condition, intra–abdominal pressure, bacteriological data were determined. Evaluation of important results was compared to the use of modern systems: APACHE–II, Mannheim Peritonitis Index (MPI), and SOFA. Indicators were evaluated on the first, second, third, fourth days after surgery until the subsequent consequences of the primary operation. All patients were distributed retrospectively and prospectively according to the Sepsis–3 classification. There were 130 with peritoneal, 33 with intestinal, 38 with pancreatogenic AS.

Surgical treatment

Surgical treatment of the analyzed patients included two main components: control of the source of infection (source control) and control of function of the affected organ and systemic protective mechanisms (damage control). Control of the source of infection: the source of infection, as well as the infections of bacteria and products involved in the inflammatory process were largely eliminated, and the choice of procedure depended on the anatomy of the source of infection, the degree of inflammation of the peritoneum, the severity of syndrome of systemic reactions to inflammation (SIRS) and multiple organ dysfunction (MODS) as well as the patient's physiological reserves. Functional damage control after sur-

gery included resuscitation, administration of solutions, antibiotics, etc. On–demand relaparotomyrelaparoscopy was performed in case of clinical deterioration of the patient or in the absence of improvement in monitoring physiological, laboratory and radiological parameters. Patients were managed by programed relaparotomy/ relaparoscopy by step–by–step remediation every 24–72 hours depending on the patient's condition until complete elimination of purulent–necrotic inflammation in the abdominal cavity, retroperitoneal space at the beginning of the final relaparotomy/relaparoscopy. The difference between the on–demand and the programmed laparotomies/laparoscopies was significantly dependent on the results of the first operation. Determination of expediency of application of relaparotomy/relaparoscopy was carried out daily during the first week. Identifying indicators for the use of relaparotomy/relaparoscopy on the second or third day was part of an on–demand strategy.

Subgroups of patients

Taking into account the surgical tactics of all patients, it was divided into three subgroups: 1 subgroup – 132 (65.7%) patients who underwent only one operation during which the source of infection was removed and there was no need to perform a relaparotomy/relaparoscopy; 2 subgroups – 42 (20.9%) patients who underwent on demand relaparotomy (30) or relaparoscopy (12); 3 subgroups – 27 (13.4%) patients, managed through surgical interventions on the program.

Statistical analyses

Statistical data were processed using the STATISTICA 13.3 EN trial software. Initially, the statistical analysis was performed using descriptive statistics. The interrelationships for interval indicators were evaluated using the criterion χ^2. The classification of the outcome of treatment using scales assessing the patient's condition was performed using ROC analysis. Traditionally, the predictive power of the scale and its discriminatory ability are based on the study of its sensitivity and specificity by calculating the area under the curve under the AUC (area under curve), taking into account its 95% confidence interval. The performance of the model was considered limited at AUC ≥ 0.70; good – at AUC ≥ 0.80; excellent – at AUC ≥ 0.90.

Results

In each groups, patients were divided into subgroups according to the severity of the condition which was determined by the criteria of Sepsis–3. To subgroup included patients with AS, above to subgroup II – with septic shock (*Table 1*). AS was diagnosed in 169 (84.4%), and septic shock was in 32 (15.9%) patients.

The results of the distribution of patients by tactical approach by severity and mortality are presented in the *Table 2*.

In the comparison group, semi–open relaparotomy procedures were performed on average 3.78±1.82 (1 to 7, median – 3.5) for 5.78 ± 2.08 days (1 to 9, median – 6), and open methods in the amount of 4.49 ± 1.47 (2 to 7, median – 4) for 6.87 ± 2.78 (1 to 12, median – 6.5). In the main group, relaparoscopy procedures were performed on average 3.14± 1.34 were performed (1 to 5, median – 3) for 4.1 ± 1.46 days (2 to 7, median – 4); open methods of relaparotomy in the amount of 3.12 ± 1.1 (from 1 to 4, median – 3) for 4.78 ± 0.96 days (from 4 to 7, median – 5).

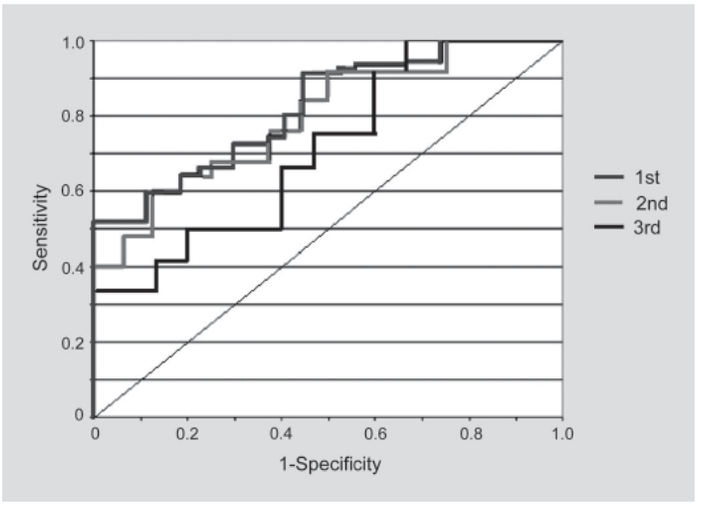
In the distribution of patients according to the method of surgical treatment, taking into account the assessment of the severity of the condition on the APACHE II score, the following values of the ROC curves were obtained: for the 1st subgroup (closed treatment) was 0.79, for the 2nd subgroups (re–operations on demand) was 0, 78, for the 3rd subgroups (programmed re–operations) was 0.71. This suggests that the score may be limited when choosing a strategy for surgical treatment in patients with AS and most likely its use will not allow a decision (good classifier in the range of 0.7–0.8) (*Figure 1*). In the distribution of patients according to the method of surgical treatment, taking into account the assessment of the severity of the condition on the SOFA score, the following

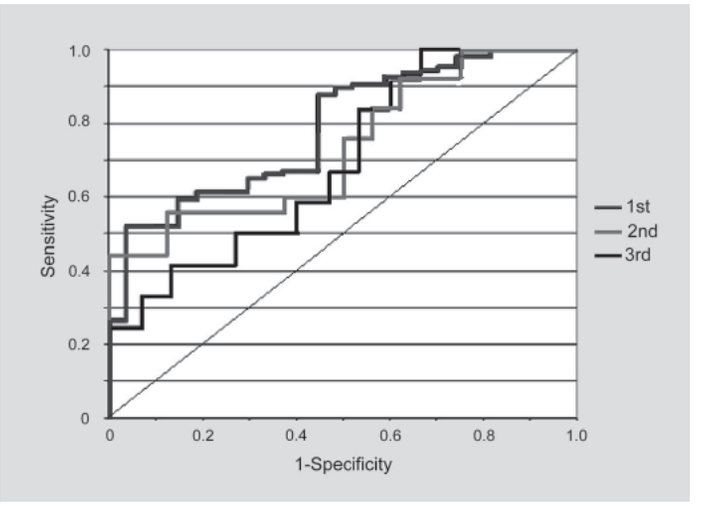
Table 1. **Distribution of patients by severity**

Groups of patients	The number of patients	The severity of the patients	
		AS	Septic shock
Comparison group	84	69 (34.3%)	15 (7.5%)
Main group	117	100 (49.8%)	17 (8.5%)
Totally	201	169 (84.1%)	32 (15.9%)
χ^2=0.404, p=0.817			

Table 2. **The results of the distribution of subgroups of patients by severity and mortality**

Groups of patients	AS	Septic shock	Died/%		Totally
The patients who used closed surgery	130	2	27	20.5%	132
The patients who have used on demand relaparotomy/ relaparoscopy	27	15	16	38.1%	42
The patients who have used programmed relaparotomy/relaparoscopy	12	15	15	55.6%	27
Died	38	20			
Totally	169	32	58	28.9%	201
Mortality	22.5%	62.5%			

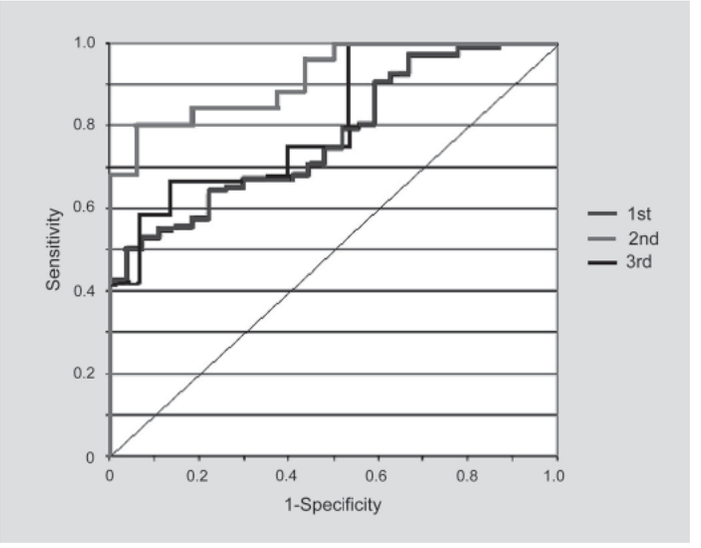




values of the ROC curves were obtained: for the 1st subgroup was 0.75, for the 2nd subgroup was 0.74, for the 3rd subgroup was 0.69 (*Figure 2*). He also points out that this scale can also be used to assess the severity of patients with AS, but will most likely not make the decision to perform surgery in these patients (a good classifier of 0.69–0.8).

In the study of patients under the method of surgical treatment, taking into account the assessment of severity of the condition by MPI, we found that this indicator is likely both for the assessment of the severity of patients with AS and for deciding whether to perform surgery in patients with sepsis and septic shock: the value of ROC–curves for the 1st subgroup was 0.73, for the 2nd subgroup was 0.91, for the 3rd subgroup was 0.84 (excellent classifier within 0.8 for two subgroups) (*Figure 3*). However, in 1 subgroup of patients (closed treatment), this indicator was 0.73, which indicates that it is limited to be used to make a decision on the performance of RL in patients without clinical signs of severe AC.

In the *Table 3* showed the postoperative complications that caused the death of patients. Postoperative complications (n=67) in the comparison group occurred in 47 patients (56%), 27 patients died (32.1%). Postoperative complications (n=37) in the main group occurred in 34 patients (29.1%), died 31 patients (26.5%) (*Table 3*). The main causes of mortality among the patients under consideration were the following: postoperative multiple organ dysfunction was in 19.9% (40 patients), persistent AS was in 5% (10 patients), intestinal fistulas due to suppuration of the wound and surgery was in 1.5% (3 patients), myocardial infarction was in 1% (2 patients) and pulmonary artery thromboembolism was in 1.5% (3 patients). The rest of the complications were managed by complex medical measures.



Discussion

Treatment of patients with AS is one of the options for surgical treatment and can be of great use in the daily treatment of seriously ill surgical patients.

At present many facts have been accumulated which indicate early activation as an anti–inflammatory response involving the formation of a septic phenotype of a number of

Table 3. **The postoperative complications in patients with AS**

The postoperative complications	Main group, n=117		Comparison group, n=84	
Postoperative MODS	26	(22.2%)	14	(16.7%)
Persistent AS	3	(2.6%)	7	(8.3%)
Suppuration of the wound and intestinal fistula	–	–	3	(3.5%)
Pulmonary artery thromboembolism	1	(0.85%)	2	(2.4%)
Myocardial infarction	1	(0.85%)	1	(1.2%)
Totally	31	(26.5%)	27	(32.1%)
χ^2=8.297, p=0.05				

pathogenesis links with the activation of triggering factors (coagulation proteins, platelets, oversaturated cells, contact activation systems (products bradykinin) and activation of the complement), changes in the microcirculation system (vasodilation and vascular permeability increase due to a decrease in systemic vascular tone and damage to the endothelium of vessels at a distance from the primary in bloodshed), tissue perfusion disorders, production of chemokines and chemoattractants with adhesion of neutrophils to the endothelium, focal necrosis (the reason for the stopping of blood flow in separate sections of the microcirculatory bed), and especially the organs of the splenic basin with neurohumoral, cardiovascular, metabolic and bioenergetic effects were found to be particularly vulnerable all of which have some prognostic significance [12–14].

For this reason the results of sepsis in patients are determined not only by the viability of pathogenic microorganisms which can be directly toxic and destructive for tissues but even more so the reaction of an organism of a sick person, which can be violent and lead to damage to tissues and organs. Over the past decades it has become evident that the immune system is more concerned about actors that cause harm than those operating from the outside referred to as endogenous anxiety molecules and hazard signals or hazard–related molecular structures (DAMP) [15]. Recent studies have confirmed that cell necrosis in contrast to trauma releases mitochondrial DNA into circulation where it can trigger inflammatory signals and molecular structures of PAMPs associated with the microbial pathogen activate congenital immunocytes through PRRs [16]. Consequently, DAMPs stimulates an acute phase reaction that is biologically consistent with PAMP released during infection. This explains why it's difficult to distinguish infectious SIRS from non–infectious or to identify individual molecules or molecular structures of the patient's response to the body that allow this distinction.

The development of endogenous intoxication in patients with AS is accompanied by a significant increase in the number of molecules that are reactive and can damage macromolecules (proteins, nucleic acids), cell membranes and intracellular organelles, as well as capable of altering intracellular. Tissue hypoxia, inhibition of the antioxidant system, separation of oxidative phosphorylation and tissue respiration, switching from aerobic to anaerobic type of energy, activation of oxidative stress, inhibition of bioenergetics, mitochondrial dysfunction, and detoxification of the pathogenic system complications in patients with AS.

Three strategies for managing these severe patients have been reported: 1) relaparotomy on demand (when required by the patient's clinical condition); 2) planned relaparotomy at 36–48 hours postoperative period (when relaparotomy is planned after the first surgery); 3) open abdominal procedure [17–19].

In 2007, van Ruler et al. published a randomized clinical trial comparing the on demand and planned relaparotomy strategy in patients with severe peritonitis. Patients in the first group did not have a significantly lower mortality rate or underlying incidence of peritonitis than patients in the second group, but they had a significant reduction in the number of recurrent laparotomies, the use of care, and medical costs [20]. The procedure of an open abdomen (laparostomy) is defined as intentional not approximation of the fascial edges of the abdomen, the abdominal contents are exposed and protected by a temporary covering [21]. When used properly, the OA technique may be useful for the treatment of surgical patients with severe abdominal sepsis and septic shock [22]. However, the role of open abdomen in the treatment of severe peritonitis is still under discussion [23]. There are currently no clinical criteria for the selection of patients for relaparotomy [24].

Previous comparisons have shown a high correlation of APACHE II with the Mannheim Peritonitis Index, as well as the fact that this index can be used to predict disease outcomes, although it does not provide an estimate for the individual patient's prognosis but is useful for the study of large groups of patients for common purulent–destructive diseases of the abdominal organs and retroperitoneal space and their complications [25].

Our research showed that the APACHE II and SOFA indicators are sensitive to determine the severity of patients but cannot be used to determine the indications for performing re–operations in patients with AS, namely the MIP is the most sensitive for determining the prognosis of treatment results and for determining indications for re–operations in the most severe categories of patients. Methods of temporary closure of the abdominal wall using negative pressure therapy have shown advantages in other methods of managing patients with the use of open abdomen with AS, which is easy to use, protects internal organs, prevents adhesions, removes exudate and prevents hypermetabolic losses according to our data.

Conclusions

1. The calculation of the probability of the patient's occurrence of postoperative complication and the probability of death depending on the initial severity of the patient's condition allows you to choose the most appropriate tactics for surgical treatment.

2. For patients with AS and septic shock, the most appropriate approach to reducing the incidence of postoperative complications and mortality is a tactical approach with repeated surgery on–demand to control the source of infection if it possible.

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Availability of data and materials

The raw data will not be made available to readers because consent for the publication of raw data was not obtained, and the raw dataset could in theory pose a threat to patient confidentiality. Due to the clinical nature of the research, the small

sample size, and the specific treatment site, the patients' identities can be easily inferred from the raw data.

Competing interests

The authors declare that they have no competing interests.

Consent to publication

All authors agreed to the publication.

Ethical approval and consent to participate

Permission for this study was obtained from the ethics committee of institution and informed consent was obtained from patients or their legal representatives.

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