ПРОБЛЕМИ ЗАГАЛЬНОЇ ХІРУРГІЇ

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Комбінована хірургічна тактика із застосуванням "step–up approach" у лікуванні інфікованого гострого панкреатиту

І. А. Криворучко[1], В. В. Бойко[2], К. Ю. Пархоменко[4], А. Г. Дроздова[1], С. А. Андреєщев[4]

[1]Харківський національний медичний університет,
[2]Інститут загальної та невідкладної хірургії імені В. Т. Зайцева НАМН України, м. Харків,
[3]Харківська обласна клінічна лікарня,
[4]Національна медична академія післядипломної освіти імені П. Л. Шупика, м. Київ

Combined surgical tactics with step–up approach in the treatment of infected acute pancreatitis

I. A. Kryvoruchko[1], V. V. Boyko[2], K. Yu. Parkhomenko[3], A. G. Drozdova[1], S. A. Andreieshchev[4]

[1]Kharkiv National Medical University,
[2]Zaitcev Institute of General and Emergency Surgery, Kharkiv,
[3]Regional Clinical Hospital, Kharkiv,
[4]Shupyk National Medical Academy of Postgraduate Education, Kyiv

Реферат

Мета. Оцінити результати лікування з використанням малоінвазивних втручань та відкритої некректомії у пацієнтів з інфікованим гострим панкреатитом.

Матеріали і методи. Ретроспективний когортний двоцентровий аналіз проведено у 211 пацієнтів з інфікованим гострим панкреатитом, які були розподілені на дві групи: 1–ша – 101 пацієнт, у лікуванні якого використовували відкриті хірургічні втручання; 2–га – 110 пацієнтів, у лікуванні яких використовували комбіновану хірургічну тактику із застосуванням step–up approach.

Результати. У 1–й групі виконали відкриту некректомію з дренуванням для післяопераційного промивання у 75 (74,3%) пацієнтів, включаючи використання лапаростомії з плановою повторною релапаротомією у 8 (7,9%) та оментобурсостомію для некрсеквестректомії після операції у 18 (17,8%). Після операції ускладнення виникли у 58 (57,4%) пацієнтів, померли 34 (33,7%) пацієнти: 30 – на 30–й, 4 – на 90–й день. У 2–й групі 72 (65,5%) пацієнтів лікували із застосуванням черезшкірного дренажу, 6 (5,5%) – за допомогою відеоасистованої заочеревинної некректомії та дренажу, 5 (4,5%) – через стінку шлунка або дванадцятипалої кишки при інфікованих псевдокистах, а відкриту некректомію виконали у 27 (24,5%) пацієнтів. Після операції ускладнення виникли у 37 (33,6%) пацієнтів, померли 19 (17,3%) пацієнтів: 15 – на 30–й, 4 – на 90-й день. Регресійний аналіз показав, що лише наявність множинної дисфункції органів до (AUC = 0,867) та після (AUC = 0,930) операції суттєво впливала на післяопераційну смертність, а вплив поширеності панкреатичного некрозу на смертність був обмеженим (AUC = 0,693). Відмінності між групами пацієнтів за цими показниками були вірогідними (χ^2=7,282, p=0,026).

Висновки. Хірургічне лікування слід розпочинати з малоінвазивних процедур, а при комбінації цих операцій з відкритими хірургічними втручаннями зменшується частота ускладнень та смертність пацієнтів з інфікованим гострим панкреатитом.

Ключові слова: інфікований гострий панкреатит; малоінвазивна хірургія; відкрита хірургія; результати.

Abstract

Objective. To evaluate the results of treatment using minimally invasive interventions and open necrectomy in patients with infected acute pancreatitis.

Materials and methods. A retrospective cohort two–centered analysis was performed in 211 patients with infected acute pancreatitis who divided into two groups: the first included 101 patients, in the treatment of which used open surgery; the second included 110 patients, in the treatment of which used treatment tactic step–up approach.

Results. In the first group used open necrosectomy with drainage for postoperative lavage (75 patients, 74.3%), including open packing with planned re–laparotomy (8 patients, 7.9%), and omentobursostomy for necrosectomy after surgery (18 patients, 17.8%). Postoperative complications occurred in 58 (57.4%), after the surgery 34 (33.7%) patients was died: 30 had a thirty–day mortality, and 4 had a ninety–day mortality. In the second group group, 72 (65.5%) patients were treated by percutaneous catheter drainage, 6 (5.5%) by video–assisted retroperitoneal debridement and drainage, 5 (4.5%) by through the wall of the stomach or duodenum in the infected pseudocyst and open necrosectomy was performed on 27 (24.5%) patients. Postoperative complications occurred in 37 (33.6%) patients, after the surgery 19 (17.3%) was died: 15 had a thirty –day mortality and 4 had a ninety–day mortality. In the regression analysis, only the presence of multiple organ dysfunction before (AUC = 0.867) and after surgery (AUC = 0.930) significantly affected postoperative mortality, but the effect of the prevalence of pancreatic necrosis (AUC = 0.693) on mortality was limited. Differences were likely between groups (χ^2=7.282, p=0.026).

Conclusion. The surgical treatment should be initiated with a minimally invasive procedures and combination these operations with open surgery was able to reduce complications and mortality in the patients with infected acute pancreatitis.

Keywords: infected acute pancreatitis; minimally invasive surgery; open surgery; results.

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal conditions worldwide, requiring acute hospital admission. The epidemiological estimates presented in the study indicate that the incidence of the disease is increasing worldwide [1]. Treatment principles of acute necrotizing pancreatitis (ANP) and the role of surgery are still controversial. Despite surgery being effective for infected pancreatic necrosis, it carries with high risk of mortality. In addition, the surviving patients often have a long–term endocrine and exocrine deficiency, which leads to a deterioration in their quality of life. Infected complications of ANP is a further factor that often leads to negative consequences is diagnosed in approximately 40% of patients and is associated with high mortality which exceeds 40% in the development of systemic complications [2]. Until recently, surgical necrosectomy was discovered by the standard treatment of infected complications of ANP. This procedure caused in prolonged multi–organ failure (MOF) and secondary local complications associated with the operation, such as bleeding, gastro–intestinal fistulas, etc. [3].

In the current International Treatment Guideline of AP in 2013 recommended a step–up approach to treatment this disease with necrosectomy as late as possible [4]. These recommendations are based on the results of the Dutch PANTER trial [5] and have been tested in other studies, such as TENSION [6] and POINTER [7]. The first step in this step–up approach is the drainage of fluid collection and complex conservative treatment with intravenous antibiotics, which can eliminate the need for any intervention in a certain percentage of patients. If this stage does not eliminate the clinical signs of infection and sepsis, the second step is performed in the form of surgical or endoscopic necrosectomy [8]. Surely, improved diagnosis and changed in the treatment of acute pancreatitis, such as minimally invasive radiologic, endoscopic and laparoscopic procedures, allow some patients completely avoid surgery and open necrosectomy, and for some of them these procedures to delay the development of sepsis when they undergo open necrosectomy, which helps reduce complications and mortality [9].

However, it is not always technically possible to implement it in daily practice especially in low economies, and there is a high risk of uncontrollable septic status with a high percentage of deaths. Percutaneous catheter drainage (PCD) of pancreatic and peripancreatic necrosis is an effective treatment option at various stages of necrotizing pancreatitis. An international survey among expert pancreatologists demonstrated 'equipoise' between immediate and postponed PCD of infected AP [10]. The aim of immediate catheter drainage is to prevent further clinical deterioration and in selected cases PCD can be used as primary therapy, but more frequently, its role serves as a temporizing measure prior to other forms of necrosectomy: endoscopic necrosectomy, open necrosectomy by laparotomy, lumbotomy, minimally invasive retroperitoneal pancreatic necrosectomy (the second step) or as an adjunct for residual fluid collections, arrosive bleeding, etc. after surgery (the third step). Numerous studies have shown that the traditional approach to surgery for infected AP in the form of pancreatic necrosectomy, followed by closed lavage, planned re–laparotomy or laparostomy, is accompanied by frequent complications, the "second hit" effect (i.e. intensification a pro–inflammatory reaction) and death [11 – 17].

The aim of this study was to evaluate the results of treatment using minimally invasive interventions compared to open necrosectomy in patients with infected acute pancreatitis.

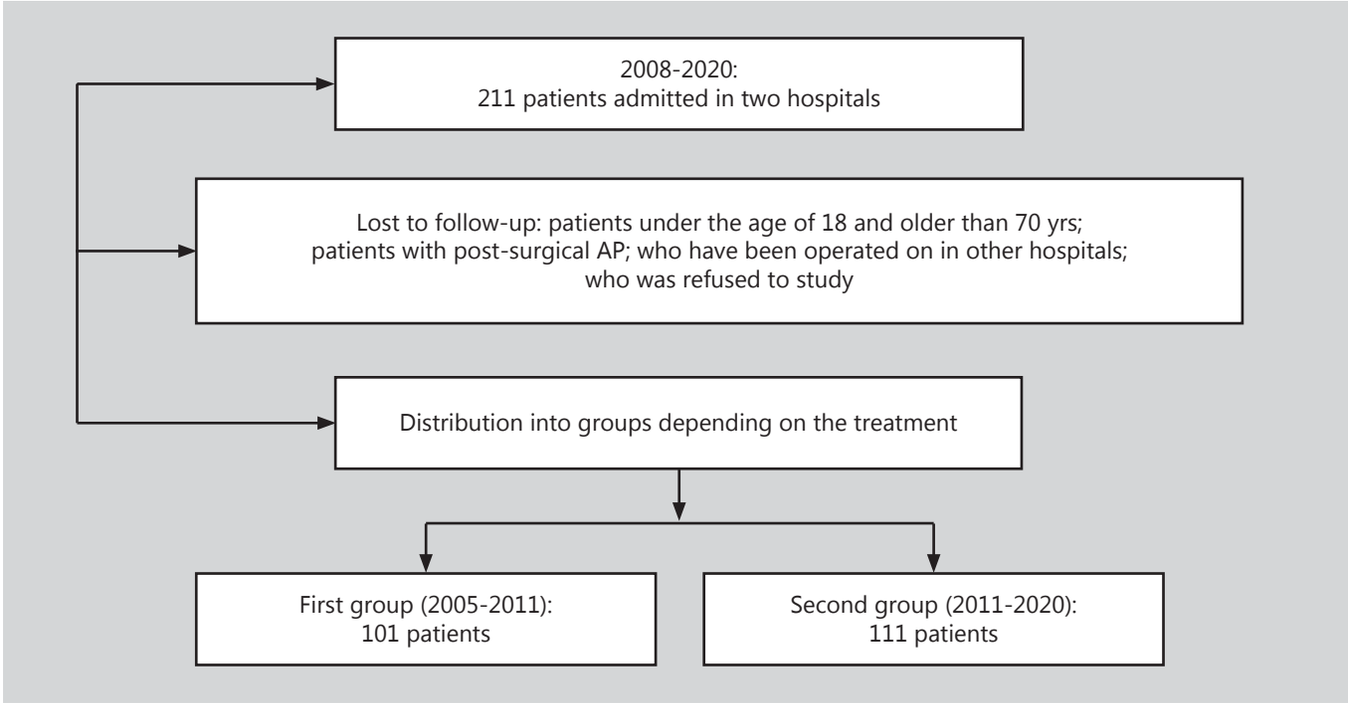

Figure 1.
Study design for patients in infected AP.

Materials and methods

Study design and patient selection

Between January 2005 and February 2020, 211 patients for severe infected AP were included: 101 before (first group) and 111 during and after January 2011 (second group). *Figure 1* presents the design for patients, who were included in a retrospective cohort two–center analysis, undergoing treatment at the Kharkiv Regional Clinical Hospital and the Zaitcev Institute of General and Emergency Surgery. We used open surgery in the treatment of patients of the first group and the tactic of step up approach in the second group. The inclusion criteria: 1) proven infected AP (7–30 days after the onset of disease) or clinical suspected infected necrosis (14–30 days after the onset of disease); 2) PCD is possible in most patients of the infected necrotic collection; 3) age ≥ 18 < 70 years. The exclusion criteria: 1) patients with post– surgery AP; 2) who was operated due to AP in other hospitals; 3) who was refused to study.

Data collection

The classification of AP was used according to the recommendations of the International Consensus (2012) [18]. Patients who was included in the study were treated in accordance with recommendations of Working Group IAP/APA (2013) adapted to our local resources and procedures. Patients' demographic data (gender, weight, height, body mass index); the characterization of the AP (etiology, the extent of the pancreatic necrosis after contrast–enhanced computed tomography (CECT); assessment of severity (Acute Physiology and Chronic Health Evaluation II (APACHE II) score) and organ dysfunction (Sequential Organ Failure Assessment (SOFA) score) by automated calculation at ClinCalc.com; the presence of infected complications of AP (clinical data, leukocytes and procalcitonin (PCT) of blood, a fine–needle aspiration (FNA) within 14 days after onset of disease); the nature of systemic complications and methods of their treatment (mechanical ventilation of the lungs, inotropic support, artificial kidney); types of surgical interventions; local postoperative complications; a thirty–day and a ninety–day mortality were evaluated.

The presence of clinical and laboratory data of infected complications of AP suspected of prolonged fever (> 38.5 °C for > 5 days) with elevated WBC and PCT (BRAHMS Aktiengesellschaft, Germany), or the emergence of a new organ failure, or gas with CECT within pancreatic and/or peripancreatic area, or in the presence of a combination of these factors [11]. The presence of gas in the pancreatic or peripancreatic

Table 1. **Main characteristics of the patients with infected AP**

Parameters	1st group (n=101)	2nd group (n=110)	$\chi^{2/p}$
Age (years), median (IQR)	51 [27–68]	48 [31–67]	0.228/0.633
BMI (kg/m^2), median (IQR)	25 [24–29]	26 [23–29]	0.000/0.993
M/F	54/47	58/52	0.012/0.994
Cause of AP, n (%):			
Metabolic	71 (70.3%)	75 (68.2%)	0.490/1.000
Biliary	26 (25.7%)	32 (29.1%)	
Others	4 (4.0%)	3 (2.7%)	
APACHE II score, median (IQR)	11 [8-17]	11 [8-18]	0.001/0.973
SOFA score, median (IQR)	12 [7-14]	12 [7-15]	0.000/0.986
Extent of the pancreatic necrosis, n (%):			
None	9 (8.9%)	19 (17.3%)	3.430/0.489
<30%	12 (11.9%)	16 (14.5%)	
30–50%	23 (22.8%)	21(19.1%)	
>50%	18 (17.8%)	24 (21.8%)	
IPN, n (%)	56 (55.4%)	63 (57.2%)	0.001/0.979
Local infected complications:			
ANC, n (%)	18 (17.2%)	25 (22.7%)	1.127/0.890
APPC, n (%)	36 (35.6%)	48 (43.6%)	
WON, n (%)	6 (5.9%)	9 (8.2%)	
PS, n (%)	12 (11.9%)	14 (12.7%)	
Transient organ failure (< 48 h):			
Single, n (%)	8 (7.9%)	6 (5.5%)	0.764/0.682
Multiple, n (%)	12 (11.9%)	16 (14.5%)	
Persistent organ failure (>48 h):			
Single, n (%)	12 (11.9%)	14 (12.7%)	0.227/0.893
Multiple, n (%):	34 (33.7%)	42 (38.2%)	
PCT (ng/ml), n (%)	26 (25.7%)	18 (16.4%)	4.222/0.320
2-10, n (%)	5 (19.2%)	6 (33.3%)	
≥ 10, n (%)	21 (80.8%)	12 (66.7%)	
Ventilation support, n (%)	18 (17.8%)	24 (21.8%)	0.180/0.671
Inotropic support , n (%)	26 (25.7%)	34 (30.9%)	0.225/0.635
Artificial kidney, n (%)	5 (4.95%)	4 (3.6%)	0.012/0.911

necrosis on CECT is considered proven infected necrosis in all patients, regardless of the disease stage (i.e. before or after 14 days). The final diagnosis infected complications of AP in a number of patients was determined after a positive microbiological investigations.

Statistical analysis

Statistical data processing was carried out using the statistical software package StatSoft Statistica 6.0. Patient demographic characteristics were described as median [interquartile range, or IQR] for quantitative variables and as number (percentage) for categorical variables. For comparison of two independent samples with non–parametric distribution used Mann–Whitney U–test, in contingency tables – χ^2. In all cases, the verification of statistical hypotheses was conducted with a confidence probability of more than 95%. To assess the adequacy of the comparisons and the accuracy of the quality of the forecast, the method of analysis of the operational characteristics curves (ROC) was used.

Results

The main data of patients of the first and second groups are presented in *Table 1*, which did not differ significantly between the two groups, and infected complications of AP was documented in similar proportions of patients in the two groups. Metabolic pancreatitis was diagnosed in 146 (69.2%) patients, biliary pancreatitis in 58 (27.5%) patients, and other origin in 7 (3.3%) patients. There were 112 (53.1%) men and 99 (46.9%) women. The average age of patients was 51 and 48, and the median of body mass index (BMI) averaged 25 and 26 kg/m^2 respectively.

The presence of infected pancreatic necrosis (IPN) was noted in 119 observations (56.4%), infected acute necrotic fluid collections (ANC) in 43 (20.4%), infected acute pancreatic/peripancreatic fluid collections (APPC) in 84 (39.8%), infected postnecrotic pseudocyst (PS) in 28 (13.3%), infected walled–off necrosis (WON) in 15 patients (7.1%). Out of 211 patients had transient organ failure in 54 (19.9%) and persistent organ failure in 102 (43.6%). It should be noted that the level of WBC was 15.7 [12.2–27.3] and 16.1 [12.8–28.2] × 10^{9}l; Lactate level was 2.4 [1.2–3.1] and 2.5 [1.4 – 3.3] mmol/l in the first and the second groups respectively.

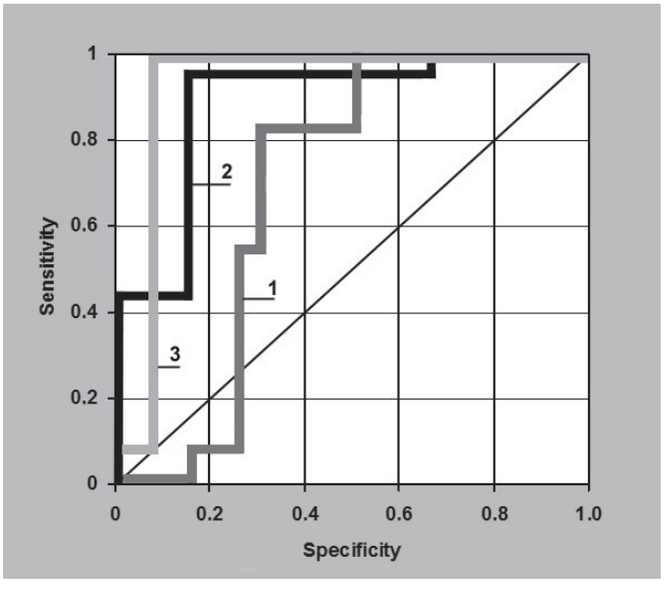

Figure 2.
ROC–curve analysis for 1) the extent of the pancreatic necrosis (AUC = 0.693, CI 0.95% – 0.583–0.745); 2) the MOF before the surgery (AUC = 0.867, 0.95% CI 0.783–0.885); 3) the MOF after surgery (AUC = 0.930, 0.95% CI 0.794–1.0).

Out of 101 patients, open necrosectomy was performed on 21 (20.8%), who operated on for the first 7–10 days, and on 80 (79.2%) patients after 2–4 weeks of the beginning of disease. The indications for open surgery were: 1) unlimited IPN in case of technical impossibility, contraindications or inefficiency of minimally invasive drainage or necrosectomy; 2) inability to correct high intra–abdominal pressure with increasing MOF. Until recently, as the standard surgical treatment of suspected or confirmed IPN we used open laparotomy (upper–middle or subcostal transverse) necrosectomy with drainage for postoperative lavage (75 patients, 74.3%), including open packing with planned re–laparotomy (8 patients, 7.9%), and omento–burso–stomy for necrosectomy after surgery (18 patients, 17.8%). Postoperative complications occurred in 58 (57.4%): bleeding in 7 (12.1%), entero–atmospheric fistula of intestine in 8 (13.8%), and MOF in 43 (74.1%) patients. Out of 4 patients with erosive bleeding, was performed angiographic hemostasis on 1 and re–laparotomy and hemostasis on 3 patients. After the surgery, 34 (33.7%) patients died: 30 (29.7%) of them had a thirty–day mortality, and 4 (3.96%) had a ninety–day mortality.

In the regression analysis (*Figure 2*), only the presence of MOF before (AUC = 0.867) and after surgery (AUC = 0.930) significantly affected postoperative mortality, but the effect of the prevalence of pancreatic necrosis (AUC = 0.693) on mortality was limited.

In the second group, 72 (65.5%) patients were treated by PCD (US–controlled – 90.3% or vidio–laparoscopy – 9.7%), 6 (5.5%) by VARDs and drainage, 5 (4.5%) by through the wall of the stomach or duodenum in the infected PS. Out of 110 patients, open necrosectomy (using laparotomy, mini–lumbotomy, upper medial, left or right–winged mini–laparotomy) was performed on 27 (24.5%) patients, who operated after 2–4 weeks of the beginning of disease, including 5 of these patients using decompressive VAC–laparostomy. Of the 72 patients with PCD, in 34 (47.2%), its use was effective, and in 27 (37.5%) additional punctures and drainage (2–4) were needed without open surgery. In 11 (15.3%) patients such procedures together with a conservative therapy allowed patients to stabilize and was performed the second step of the treatment using low–traumatic operations: local laparotomy or lumbotomy in 6 and VARDs in 3 patients. Postoperative complications occurred in 37 (33.6%) patients: erosive bleeding in 3 (8.1%), residual or newly formed intra–abdominal collections of purulent fluid in 5 (13.5%), entero–atmospheric fistula of intestine in 1 (2.7%), and MOF in 24 patients (64.8%). In 3 patients with erosive bleeding was executed successfully angiographic hemostasis (the third step) and repeated punc-

Table 2. **The results of the treatment of patients**

Parameters	1st group (n=101)	2nd group (n=110)	$\chi^{2/p}$
Postoperative complications, n (%)	58 (57.4%)	37 (33.6%)	4.049/0.044
Hospital stay of discharged patients (days), median (IQR)	45 [18-83]	34 [16-56]	1.555/0.212
Thirty-day mortality, n(%)	30 (29.7%)	15 (13.6%)	4.521/0.033
Ninety-day mortality, n(%)	4 (3.96%)	4 (3.6%)	0.059/0.809
Total amount, n (%)	34 (33.7%)	19 (17.3%)	3.867/0.049
Of them:			
without MOF, n (%)	4 (11.8%)	8 (42.1%)	6.406/0.041
with MOF, n (%)	30 (88.2%)	11 (57.9%)	

tures collections of purulent fluid under US control. After the surgery 19 (17.3%) patients died: 15 (13.6%) of them had a thirty–day mortality and 4 (3.6%) had a ninety–day mortality.

In *Table 2* demonstrated that differences were likely between groups in terms of complications and overall mortality (χ^2=7.282, p=0.026).

Discussion

The surgical treatment of infected complications of AP continues to evolve and now includes several alternatives to traditional open surgical treatment – minimally invasive strategies have been developed to reduce the stress associated with open surgery. It known, that the principles of surgical management for pancreatic necrosis have been developed by B. Moynihan [19] and the main surgical methods for controlling of infected complications of AP and sepsis included over the past 30 – 40 years: 1) closed–suction technique with necrosectomy, drainage for postoperative lavage [12] or without it [13]; 2) open packing with planned re–laparotomy and serial debridements [14, 16], and modifications of these methods [17]. Given the fact that necrotizing pancreatitis remains a serious disease associated with significant morbidity and mortality, and necrosis infection is a major risk factor for MOF and almost 100% mortality in the second phase of this disease due to the inability full control the source of infection and MOF in these patients after the open intervention, recommendations have been revised for the treatment methods over the past decades, and there are various minimally invasive interventions as an alternative to traditional open necrosectomy. These include minimally invasive retroperitoneal pancreatic necrosectomy [20 – 22], laparoscopic necrosectomy [22], endoscopic necrosectomy [23, 24], and various percutaneous approaches, used alone or in combination with other techniques [25, 26].

It has been suggested that percutaneous drainage of the focus of infection of the pancreas and fluid collections can have a positive therapeutic effect. This recommendation was based on clinical observations that showed no need for the maximum removal of all necrotic tissues for successful of IPN patients [27]. By drainage of infected fluid focus, the authors have shown that the clinical state of patients may improve after these interventions, and necrotic tissues can be successfully treated in the subsequent immune system of the patient. Subsequently, reports appeared on the effectiveness of drainage of pancreatic/peripancreatic fluid accumulations in AP, which was manifested in an improvement in the clinical status of patients after these interventions [28].That is, the purpose of drainage is the removal of infected fluid but not necrosis. But these published reports are generally single institution series, and there was considerable heterogeneity of technique even within each modality.

Our study specifically compared two strategies and it does provide a direct comparison of open necrosectomy with minimally invasive treatment of infected AP. The analysis of the management results of the patients we examined showed that in both groups the surgical treatment was selected in a different way, individually, in accordance with the phases and characteristics of the course of the disease. Complete data on organ support therapy were available for the 111 patients admitted directly to ICU: 49 were admitted in the first group and 62 in the second group (*Table 1*). The number of patients with inotropic, ventilation support and artificial kidney by day 30 was unreliable in both groups, although the duration of organ support therapy was shorter in the second group.

In patients of the first group open necrosectomy was performed in all patients. In the second group of patients, surgical was performed sequentially, starting with the least invasive methods: puncture, puncture–draining transcutaneous and endoscopic. When comparing the two strategies of treatment tactical approach we have established that in the second group of patients where the principles of step–up approach were used for the diagnosis and treatment of infected complications of AP, the number of postoperative complications and mortality were lower than in the group of patients which performed only open surgical intervention (*Table 2*). When comparing treatment methods in the two groups, significant differences were found in the number of postoperative complications and overall mortality (χ^2=7.282, p=0.026).

Thus, the minimally invasive techniques to be promising methods for the treatment of infected complications of AP and should be performed in specialised hospitals with expertise in the management of severe AP and the hybrid treatments for this category of patients. The choice of a minimally invasive procedure depends on many factors, including the availability of qualified specialists in various fields of medicine.

Conclusion

Endoscopic treatment used preferably in patients with the necrotic collections limited, and in patients who require in-

tervention at the later stages of disease when the necrosis is well liquefied. Retroperitoneal, minimally invasive necrosectomy to be an interesting technique for the treatment of patients with large necrotic collections extending down to the retrocolic regions and also after adequate liquefaction of the necrosis. Local laparotomy or lumbotomy could performed options with infected fluid collections in the absence of the ability to perform PCD in patients with infected WON and also infected PS. Although the results of minimally invasive techniques are encouraging, their use shouldn't lead to a delay in appropriate treatment. Lack of clinical improvement may be an indication for open necrosectomy which is the preferred choice in situations was complicated by abdominal compartment syndrome, colon ischaemia and bowel perforation. On the other hand, percutaneous or endoscopic drainage might be life saving to most patients, and especially by those patients who are in critically ill.

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Informed consent process. Informed consent was obtained from all participants included in the study.

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