

# Is minimally invasive surgical treatment justified for severe acute necrotizing pancreatitis patients with dysfunction of two or more organ systems?

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Videosurgery Miniinv 2017; 12 (3): 225–230  
DOI: <https://doi.org/10.5114/witm.2017.68792>

## Abstract

**Introduction:** When minimally invasive therapy was introduced, it became possible to cure some patients without open surgery, or at least delay the operation for longer than a month.

**Aim:** To determine the optimal timing to operate on patients with severe acute necrotizing pancreatitis based on the severity of organ insufficiency.

**Material and methods:** A retrospective analysis was performed in all severe acute necrotizing pancreatitis patients treated in Vilnius University Hospital Santaros Klinikos (VUL SK) from 2007 to 2016. The patients were divided into groups based on the number of dysfunctional organ systems (one or more) and whether the minimally invasive step-up approach to treatment was used.

**Results:** The patients with one organ dysfunction had a delay of 35 (without the step-up approach) and 36 (with the step-up approach) days before the open surgery, while the patients with two or more organ systems' dysfunction had almost an identical delay of 28 days, using both surgical treatment methods. The mortality of the patients who had one organ dysfunction and in whom the step-up approach was used was 0%, while in patients without the step-up approach it was 41.7%. In the two or more organ systems' dysfunction group, the mortality for those treated with a step-up approach was 64.3%, and without it 70.7%.

**Conclusions:** The surgical treatment should be initiated with a minimally invasive procedure. Additionally, the surgery on patients with two or more organ systems' dysfunction should not be delayed for more than one month.

**Key words:** severe necrotizing pancreatitis, open necrosectomy, minimally invasive surgery.

## Introduction

A breaking point in the treatment of patients with severe acute necrotizing pancreatitis has been reached, moving from early surgical intervention to maintenance therapy, within the first 2 weeks of the onset of symptoms. It was started after several studies showed high morbidity with early surgical interventions. The authors of one prospective ran-

domized study reported that the mortality rate was 58% for patients who underwent surgery within 42–72 h after the onset of symptoms, and the patients who underwent surgery after more than 12 days from the onset of symptoms had a mortality rate of 27% [1]. Other studies confirmed these results, but some authors have suggested that surgery should be delayed for at least a month or longer from the onset

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of the disease, and it should be performed only if acute necrotizing pancreatitis infection is confirmed and/or the pain continues, and the current patient condition would not allow one to wait for the inflammatory process to subside [2, 3].

The improvements of radiology diagnostics and changes of treatment methods of the disease, such as minimally invasive radiologic, endoscopic and laparoscopic procedures, allowed for some patients to completely avoid the surgery and open necrosectomy [4, 5], and for some to delay the onset of sepsis and undergo open necrosectomy even in the 6<sup>th</sup> or 8<sup>th</sup> week, which decreases the mortality rate. However, the majority of international treatment guidelines recommend performing open surgical necrosectomy in the 4<sup>th</sup> week [6–8].

It has also been claimed that acute necrotizing pancreatitis surgical treatment will become obsolete. Despite the new critical care technologies, such as extracorporeal cytokine filtering and extracorporeal membrane oxygenation, and deeper knowledge of pancreatitis, such as the progress of the disease and progress of the minimally invasive approach, the need for open surgery still exists. Now, a lot of centres are using the step-up approach based on the PANTER study, published in 2010, which resulted in other minimally invasive technique studies, like TENSION, PUINGUIN and POINTER. Vilnius University Hospital Santaros Klinikos also uses the step-up approach [9]. However, it is not always technically possible to implement it in daily practice, and there is a high risk of uncontrollable septic status.

Due to continuous discussion on when it is best to operate on patients with acute necrotizing pancreatitis, Vilnius University Hospital Santaros Klinikos conducted a retrospective study of the patients treated in the clinic, by comparing the treatment results with the timing of the surgical intervention, hoping to find out the optimal time for surgical treatment in acute necrotizing pancreatitis.

## Material and methods

A retrospective cohort analysis was performed, in which all patients treated in VUL SK from 2007 to 2016 for severe acute pancreatitis were selected. Patients were evaluated based on the updated Atlanta classification [10], and the ones who underwent surgical treatment were singled out. Only those patients who were treated from 2007, developed one

or several organ systems' dysfunction within the first 3 days, and underwent open surgery were analysed. These patients were divided into groups based on whether the step-up approach was used or not. The purpose of dividing patients into the groups was to determine which group of patients benefits from the step-up approach. Patients' demographic data, time until the open surgery, duration of hospitalization, pancreatic and surrounding tissue changes according to computed tomography severity index (CTSI) [11], postoperative complications, and mortality were evaluated. Also, the results of microbiological culture, obtained during the first surgery, were analysed.

Patients were also divided based on the indications for surgical interventions: 1) had surgery within 2 weeks after the onset of the disease due to systemic inflammatory response complications (mesenteric artery thrombosis, hollow organ perforation, uncontrolled intra-abdominal hypertension, bleeding), emphysematous pancreatitis, iatrogenic pancreatitis (ERCP, post-surgical), 2) when the minimally invasive surgery or open surgery was performed at least 15 days from the onset of the disease due to infected necrosis, proved by fine needle aspiration biopsy (FNA), or radiologically and clinically worsening patient's condition.

Data were processed with SPSS 23 and MS Excel 2013 programs. To conduct the research, permit No. EK-13 (2016.03.03) was obtained from Vilnius University Hospital Santaros Klinikos Clinics' Ethics Committee.

## Results

There were a total of 325 patients treated in Vilnius University Hospital Santaros Klinikos (VUL SK) for severe acute necrotizing pancreatitis from 2007 to 2016 (within 10 years).

Metabolic pancreatitis was diagnosed in 210 (64.6%) patients, biliary pancreatitis in 104 (32%) patients, and other origin in 11 (3.4%) patients. There were 198 (60.9%) men and 117 (39.1%) women. The average age of men was  $51.1 \pm 17.6$  and of women  $60.0 \pm 16.7$ .

Out of 325 patients who had severe acute pancreatitis, local complications without organ dysfunction were observed in only 54 (16.6%) patients.

There were 271 (83.4%) patients with organ system dysfunction: 101 (31.1%) patients had one organ dysfunction with local complications, and 170

**Table I.** Patients' mortality depending on organ systems' dysfunction

Variable	One organ system dysfunction				Two or more organ systems' dysfunction			
	Treated conservatively	Op. < 2 weeks	Op. > 2 weeks	Total	Treated conservatively	Op. < 2 weeks	Op. > 2 weeks	Total
Patients	48	27	26	101	57	44	69	170
Deaths	0	7 (6.9%)	5 (4.9%)	12 (11.8%)	15 (8.8%)	24 (14.1%)	47 (27.6%)	86 (50.6%)

(52.3%) patients had two or more organ systems' dysfunction with local complications (Table I).

In patients with one organ system dysfunction the overall mortality rate was 11.8%, and in those with two or more organ systems' dysfunction it was 50.6%.

Upon analysing the mortality of patients having one organ system dysfunction, it was found that the mortality rate was similar: 25.9% of those operated on within the first 2 weeks due to iatrogenic complications or complications caused by systemic inflammatory response; and 19.2% when the surgery was performed later because of the patient's septic status.

Comparing the mortality of patients with two or more organ systems' dysfunction, higher mortality rates were observed in those who were operated on later due to septic complications (68.1%) vs. those operated on within 2 (54.4%) weeks.

Out of 95 patients a step-up approach to treatment was used on 42 (44.2%) patients. Open necrosectomy was performed on 53 (55.8%) patients. In the step-up group, the sonoscopic drainage was performed on 28 (66.7%) patients, retroperitoneal necrosectomy on 14 (33.3%), and both sonoscopic drainage and retroperitoneal necrosectomy on 5 (11.9%) patients.

By comparing these groups, it was concluded that male to female ratio, computed tomography severity index (CTSI), the number of reoperations and complications, and overall hospitalization length of survived patients were not different. The rate of microbiologically proven infected pancreatic necrosis was not significantly different: in the step-up group 85.7%, and in the operated patients' (no step-up) group 79.2% (Table II).

**Table II.** Patients treated with the step-up approach, and patients who had necrosectomy without a step-up

Parameter	Treated by step-up approach technique		Treated without step-up approach technique		P-value
Number of patients	42	45.7%	53	54.4%	
Gender:					
Women	15	35.7%	19	35.9%	
Men	27	64.3%	34	64.2%	
Average age [years]	47.5 ±15.4		56.5 ±16.1		0.050
2 or more organs' dysfunction	28	66.7%	41	77.4%	
CTSI	7.9 ±1.7		7.6 ±1.9		0.597
2 or more operations	2.6 ±1.9		2.7 ±2.2		0.850
Hospital stay of discharged patients [days]	91.3 ±39.1		97.2 ±33.2		0.599
Preoperative time [days]	32.5 ±19.2		28.8 ±14.0		0.626
Complications (fistulas, bleeding, or both)	19	45.2%	38	71.7%	0.150
Infection of pancreatic necrosis	85.7%		79.3%		0.311
Mortality	18	42.9%	34	64.2%	0.0116



So, the new challenge is to change the tactics of the surgical intervention, hoping to decrease the mortality from septic complications: start using the step-up approach widely and delay the surgery for as long as possible.

In 2010 *New England Journal of Medicine* published the PANTER study – the minimally invasive step-up approach compared with open necrosectomy in patients with severe necrotizing pancreatitis. The benefits of this multicenter study are: using minimally invasive methods in comparison with open necrosectomy, and decreasing the number of major complications in patients who had severe acute necrotizing pancreatitis and infected necrosis [18].

The PANTER study showed that the mortality in the groups did not differ significantly (19% of patients with open necrosectomy, and 16% with the step-up approach). But MODS develops more rarely in the step-up approach, 12% vs. 40% [18].

The PINGUIN study showed that when applying TENSION (transluminal endoscopic necrosectomy), the SIRS decreases: IL6 concentration in the blood decreases in comparison to minimally invasive surgery. Development of MODS – 0% vs. 50%, and less pancreatic fistulas, 10% vs. 70% [8].

However, our analysis of the results showed that the step-up approach is only effective for the severe acute necrotizing pancreatitis patients with one organ dysfunction. There was a statistically significant decrease of mortality. In patients with two or more organ systems' dysfunction, we did not find any statistically significant decrease in mortality, but there is a probability of 50%.

Another possibility to increase the survival rate is to delay the surgery as much as possible. International guidelines recommend delaying catheter drainage up to 4 weeks from the onset of symptoms until the necrotic masses separate. However, we had to perform the minimally invasive interventions in patients with proven pancreatic necrosis infection earlier. The indications for intervention in a sterile necrotizing pancreatitis (4–8 weeks from the onset of symptoms) are: persistent gastrostasis, caused by pancreatic and/or peripancreatic tissue oedema due to acute pancreatitis, intestinal or biliary obstruction, other persisting symptoms such as pain and shutting pancreatic syndrome [19].

What is the optimal time for intervention? It is stated that the interventions should be avoided within 2 weeks of the onset of severe acute necro-

tizing pancreatitis. During this period, a lot of patients may require intensive treatment in the intensive care unit due to progressive organ dysfunction, which is associated with high mortality [20]. Early intervention in the pancreatic or peripancreatic inflamed tissues does not increase the survival rate. There are rare exceptions, when surgical treatment is needed: intra-abdominal bleeding, intestinal necrosis. In any case, if it is at all possible, it is best not to touch the inflamed pancreas in the first 2 weeks [21]. Pancreatic necrosis usually separates within 3–5 weeks from the onset of symptoms. Several observational studies have indicated that a better solution would be to perform the surgery more than 28 days after the onset of the disease [21, 22]. Some authors state that delaying the surgery for more than 28 days worsens the overall condition of the body due to nutritional and immune deficiency.

Antibiotics can delay the onset of infected necrosis intervention by up to 4 weeks [23]. Indications for the intervention are: suspected or confirmed necrotic infection, persisting organ dysfunction for several weeks without signs of infection, demarcated infected necrosis, pain or ileus [24]. It was discussed whether by applying the step-up approach it is possible to delay the necrosectomy time by 6–8 weeks. However, data from some studies show that after 6–8 weeks festering occurs, and it can be difficult to open the abscess [25].

All our data showed that delaying surgery is only possible in the patients with one organ system dysfunction, whether the step-up approach was used or not. Patients with the step-up approach survived.

In patients with two or more organ systems' dysfunction, whether the step-up approach was successful or not, our surgery was performed on the 28<sup>th</sup> day and the mortality was almost the same in both groups – 70%. Also, infected pancreatic necrosis was confirmed in 85.7% of all step-up approach patients. The minimally invasive surgical treatment was not sufficient for any patients. All of them had to undergo open surgery.

## Conclusions

After analysis of our findings, we concluded that the main factor determining mortality is the severity of organ dysfunction, and all efforts need to be directed toward its prevention and appropriate treatment. The step-up approach improves surviv-

al in patients with one organ system dysfunction. The step-up approach is not as effective in patients with two or more organ systems' dysfunction, and it is only technically possible in 50% of Lithuanian patients. Despite this, the surgical treatment should be initiated with a minimally invasive procedure if possible. In patients with two or more organs' dysfunction, the surgery should not be delayed for more than one month.

## Conflict of interest

The authors declare no conflict of interest.

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Received: 19.04.2017, accepted: 31.05.2017.