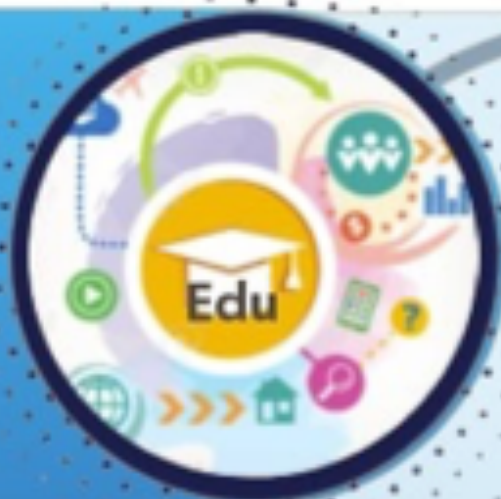


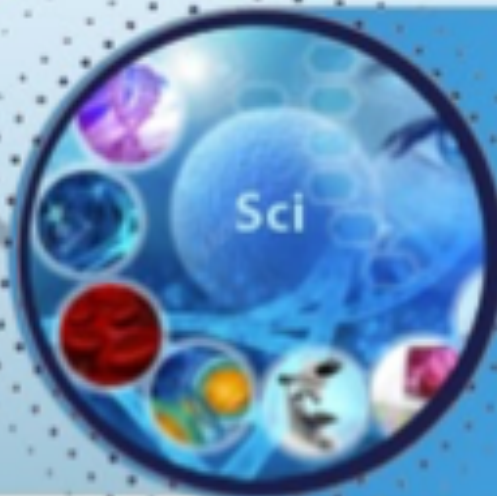


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# Diagnosis and Treatment of Pancreatogenic Sepsis

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## ABSTRACT

Difficulties in choosing therapeutic and diagnostic tactics for acute pancreatitis are due to the multivector features of the course of this disease. The issues of choosing diagnostic methods and methods of treatment for uncomplicated and complicated, severe and mild pancreatitis, the so-called "edematous" pancreatitis and pancreatic necrosis, complications of pancreatogenic toxemia and destructive complications, sterile and infected pancreatic necrosis, early infection and late destructive complications are discussed.

**Key words:** Pancreatic necrosis, pancreatogenic sepsis, diagnosis and treatment

## INTRODUCTION

In our time, it is difficult to find a more complex inflammatory disease of the abdominal organs in its pathogenesis than acute pancreatitis. Over the past 50 years, acute pancreatitis ranks third among acute surgical diseases of the abdominal cavity and accounts for about 12.5% of all urgent pathology. [2, 5]

At the same time, diagnostics and surgical tactics for pancreatic necrosis remain in our time one of the far from solved problems in urgent abdominal surgery. There is no doubt that this problem is related to the difficulties of prognosis and early diagnosis of destructive forms of acute pancreatitis. [3, 4, 6]

Also, the relevance of the problem is due to the frequency of acute pancreatitis in the majority of patients (65–70%) at working age. At the same time, in the case of the development of pancreatic necrosis and the use of surgical methods of treatment, disability is noted in more than half of patients - from 62.8 to 75.3% of cases. All this also gives the problem socio-economic significance. [11]

The mechanism of pathogenesis of acute pancreatitis is multifaceted. And despite the fact that 80-90% of acute pancreatitis manifests itself in the form of mild inflammation with a low number of deaths, severe forms of this disease, with progressive systemic inflammatory response syndrome and pancreatic necrosis, are potentially fatal and form the basis of fatal outcomes. [1] At

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the same time, the basis of lethal outcomes in infected forms of pancreatic necrosis is formed by cases of sepsis and organ failure. For example, the overall mortality rate for pancreatic necrosis is 3.9–26%, and for infected pancreatic necrosis – up to 85%, for fulminant disease – 100%. [10]

Difficulties in choosing therapeutic and diagnostic tactics for acute pancreatitis are due to the multivector features of the course of this disease. The issues of choosing diagnostic methods and methods of treatment for uncomplicated and complicated, severe and mild pancreatitis, the so-called "edematous" pancreatitis and pancreatic necrosis, complications of pancreatogenic toxemia and destructive complications, sterile and infected pancreatic necrosis, early infection and late destructive complications are discussed.

At the same time, dissimilar, and often opposite opinions are expressed on the same issue. [8, 9]

In the treatment of pancreatic necrosis complicated by sepsis, many attempts are made to study the effect of conservative therapy on the course of the disease. Particular attention should be paid to the work on the effect of anticytokine therapy in pancreatic necrosis to prevent the development of sepsis. [7, 10]

## MATERIAL AND METHODS

A retrospective cohort study of the results of comprehensive examination and treatment of 97 patients with pancreatic necrosis complicated by sepsis for the period 2013-2017 was carried out.

In 38 (39.18%) cases, pancreatic necrosis was sterile, and in the remaining 59 (60.82%) cases, it was infected. At the same time, among patients with infected pancreatic necrosis, in 20.62% of cases, infected pancreatic necrosis occurred against the background of severe sepsis, and in 4.12% of cases – septic shock. Thus, the patients were divided into 3 groups: the first group consisted of patients with sterile pancreatic necrosis (38 patients; 39.18%); the second group included patients with infected pancreatic necrosis (35 patients; 36.08%); the third group consisted of patients with infected pancreatic necrosis complicated by sepsis (24 patients; 24.74%).

There were 62.9% of male patients and 37.1% of female patients. Both among men (52.5%) and among women (50.0%), patients in the age category from 41 to 50 years prevailed (in the total value of 51.5%). In second place were patients in the age category from 51 to 60 years (26.8%) and third place - from 31 to 40 years (11.3%). Thus, this analyzed parameter of patients

showed that the basic contingent fell on patients of the most able-bodied mature age.

Alcohol etiology of the disease accounted for 28.9% of patients. In 43 (44.3%) patients, cholelithiasis was the cause of pancreatic necrosis. The gastrogenic origin of the disease was revealed in 25 (25.8%) patients. In 1 patient (1.03%), the etiological cause of pancreatic necrosis could not be determined.

Patients' visits to the clinic from the onset of the disease were not unambiguous, but there was a certain pattern among the groups. For example, in the first group of patients, patients who came before 12 hours from the onset of a pain attack prevailed (86.8%). Further, to a lesser extent, there were patients who came to the clinic before 1 day after the onset of the disease (13.2%).

Among the patients of the second group, the peak of treatment occurred on 2-3 days after the onset of the disease (80.0%). The rest of the patients came either 2 days earlier (17.1%) or 2 days later (2.9%). Nevertheless, the main flow of patients in this group fell on the period of time from 1 to 3 days from the onset of the disease.

Patients of the third group went to the clinic after the onset of the disease for 4-10 or more days. The distribution of chronology in this interval in this group of patients indicated that pancreatic necrosis complicated by sepsis is characteristic of patients who come to the clinic for more than 10 days of the disease.

Summarizing and drawing parallels between the chronological intervals of the onset of the disease and hospitalization in the clinic, it can be stated that in the interval up to 12 o'clock, 100% of cases accounted for patients of the first group. In the intervals up to 24 hours from the onset of the disease, 54.5% of patients of the second group and 45.5% of patients of the first group were hospitalized.

Within 2-3 days from the onset of the disease, all hospitalized patients were in the second group. Only starting from 4-5 days from the onset of the disease, patients of the third group prevailed in hospitalization, amounting to 87.5%. At the same time, the rest of the contingent of patients accounted for patients of the second group (12.5%). Later, the patients who came to the clinic were from the third group.

## RESULTS AND DISCUSSION

According to archival data, acute pancreatitis was established only in 68 (71.1%) patients. In the remaining cases (28.9%), before hospitalization in our clinic, diagnoses of acute cholecystitis (15.5%), perforation of gas-

trooduodenal ulcer (7.2%), acute intestinal obstruction (4.1%) and acute appendicitis (3.1%) were established.

At the time of hospitalization, 687 pathological signs were described in the medical history. Of these, 26.6% were patients of the first group, 39.7% of patients of the second group, and 33.6% of patients of the third group.

The distribution of these pathological signs showed that pain syndrome was prevalent (it was noted in all 100% of cases). Pain was localized in the epigastrium, right or left hypochondrium, in most cases the pain radiated to the left costovertebral angle, and then in descending order to the left shoulder, behind the sternum, between the shoulder blades. Pain was the flagship among the pathological manifestations of the disease in all the analyzed groups.

Dyspeptic disorders are a constant companion of destructive pancreatitis. They were in second place in terms of the frequency of registration after pain syndrome and accounted for 93.8%. Among the varieties of dyspeptic disorders, nausea, uncontrollable vomiting that did not bring relief, constipation, flatulence and bloating prevailed. At the same time, in the second and third groups, this symptom complex was noted in all patients, while in patients of the first group, they bothered patients only in 84.2% of cases.

Local symptoms of acute pancreatitis were positive in 90.7% of cases. Local symptoms characteristic of acute pancreatitis occurred in all patients. Tension of the muscles of the anterior abdominal wall and symptoms of peritoneal irritation in 100% of cases were noted in patients of the second and third groups, while among the patients of the first group they occurred only in 29 (76.3%) patients.

Almost half of patients with destructive pancreatitis (43.3%) had ictericity of the sclera and skin at admission. There were 34.2% of patients in the first group, 40.0% of patients in the second group, and 62.5% of patients in the third group.

Pathological signs from the cardiovascular system were in the form of tachycardia, recorded in 90.7% of cases, and a decrease in systolic blood pressure below 100 mm Hg. st. in 68.0% of patients. Tachycardia in 100% of cases was recorded among patients of the second and third groups, while in patients of the first group, an increase in heart rate was registered only in 76.3% of cases. It should be noted that tachycardia and a decrease in systolic blood pressure were noted by us in the early stages of the development of destructive pancreatitis.

An increase in body temperature above 37 °C was recorded in 75 (77.3%) cases. At the same time, among

the patients of the second and third groups, as in the previous case, hyperthermia was noted in all cases, while in the patients of the first group only in 16 (42.1%) cases.

Respiratory disorders were noted in 70 (72.2%) patients. In the first group, there were 36.8% of patients with dyspnea, 91.4% in the second group, and 100% in the third group.

The revealed pathological manifestations of the genitourinary system were presented in the form of hematuria, proteinuria, cylindruria or a combination thereof. In general, 37 (38.1%) patients had such disorders. There was only one patient in the first group, 12 (34.3%) patients in the second group, and all 24 patients in the third group.

Mental and nervous system disorders were detected at admission in 33 (34.0%) patients. They manifested themselves in 22 (22.7%) patients in the form of euphoria, anxiety and negativism. Psychomotor excitations and hallucinations were diagnosed in 9 (9.3%) patients. Acute depression of the psyche, sometimes up to a comatose state, was diagnosed in 2 (2.1%) patients.

It should be noted that among the patients of the first group, we did not diagnose such disorders. Among the patients of the second group, such changes were revealed in 9 (25.7%) patients, and in patients of the third group in 24 patients (that is, in all cases).

We actively used laparoscopic technologies in the verification of pancreatic lesions. Diagnostic laparoscopy was performed in 48 (49.5%) patients. On day 1 of hospitalization, it was used in 19 patients, on day 2 in 10 patients, on day 3 in 8 patients, on day 4 in 7 patients, and on day 5 in 4 patients. The average duration of this intervention was  $3.1 \pm 1.1$  days.

Clinical and morphological parallels in patients revealed a predominance of patients with total (32.0%) and subtotal (26.8%) necrotic lesions of the pancreas. In subtotal lesions, the predominant lesions were of the head and body of the pancreas. In 40 (41.2%) patients, necrotic lesions of the pancreas were focal. At the same time, in 21.6% of cases - large-focal, and in 19.6% of cases - small-focal lesions.

A comparative analysis between sterile and infected forms of pancreatic necrosis revealed that in the first case, focal (13.9 times), and in the second case, widespread (46.6 times) necrotic lesions of the pancreas prevailed.

The mean severity of acute pancreatic necrosis was  $8.4 \pm 1.1$  points.

The variance of the mean value decreased from  $10.1 \pm 0.9$  points in total pancreatic necrosis to  $6.8 \pm 2.9$

points in small-focal pancreatic necrosis ( $p < 0.05$ ). In the infected form of pancreatic necrosis, the lesion severity index was  $1.9 \pm 0.3$  points higher than in patients with sterile pancreatic necrosis ( $p < 0.05$ ).

We mainly used active surgical tactics, consisting of early laparotomy, despite the phase (sterile or infected) of the pathological process and the form (small-focal, large-focal, subtotal, total) of necrotic lesions.

The main indications for surgical operations were the negative dynamics of the disease despite conservative therapy and/or the presence of signs of peritonitis.

If laparotomy was performed in the sterile phase of pancreatic necrosis, the abdominal organs were revised at the first stage. If the development of pancreatic necrosis was suspected, the omental bursa was opened and a visual revision was performed. The operation ended with sanitation and drainage of the omental bursa and abdominal cavity with several drains. In the presence of dead areas of the pancreas, necrotic tissues were removed in a blunt and acute way. Such a procedure was sometimes very dangerous due to the possible development of arrosive bleeding or the formation of digestive fistulas. With the biliary origin of pancreatic necrosis, interventions were performed on the gallbladder and bile ducts.

In infected pancreatic necrosis, the main goal of laparotomy was to perform necrosectomy in a timely and complete manner, drainage of purulent cavities of parapancreatic tissue for subsequent sanitation. They opened the omentum bursa, all possible formed cavities that were filled with pus. Necrotic tissues of the pancreas and retroperitoneal space were removed in a blunt and sharp way. The latter was necessarily subjected to a thorough finger revision. Drainage was carried out in the area of the retroperitoneal space, omentum bursa, abdominal cavity.

As can be seen from the description of the course of surgical interventions, there were several varieties per patient. In total, 451 surgical interventions were performed according to the protocols of operations. At the same time, an average of  $4.6 \pm 1.1$  technical stages were performed for each patient. The leaders in these stages were drainage interventions (215), which amounted to 47.6%. At the same time, in 23.9% of cases, the omental bursa was drained and in 23.7% of cases, the abdominal cavity was drained. It should be noted that drainage of the abdominal cavity was performed without drainage of the omentum bursa. But drainage of the omentum bag was carried out repeatedly, which causes the difference in values.

Necrosectomy was performed in 13.7% of cases (62 times). Omentobursotomy and marsupialization of the omental bursa were performed in 13.5% of cases (61 times). Parapancreatic cell drainage was performed 48 times (10.6%).

Interventions in cholelithiasis were reduced to cholecystostomy (1.3%) and cholecystectomy with drainage of the bile ducts (8.2%).

In 22 (4.9%) cases, the suppurated pancreatic cyst was opened and drained.

The volume and nature of surgical interventions performed in the section of the phase of pancreatic necrosis showed a 4.4-fold prevalence in patients with infected pancreatic necrosis. In the phase of sterile pancreatic necrosis, there were an average of  $2.2 \pm 1.0$  types of surgical intervention per patient, and in the phase of infection, this value was 2.8 times higher.

Analysis of the distribution of surgical interventions performed in the sterile phase of pancreatic necrosis depending on the morphostructural nature of the pancreatic lesion showed that drainage surgical interventions prevailed in small-focal and large-focal pancreatic necrosis. In subtotal pancreatic lesions, the volume of surgical interventions was evenly distributed between drainage of the abdominal cavity, drainage of the omental bursa, cholecystostomy, cholecystectomy with drainage of the ducts, and omentoburostomy with marsupialization of the omental bursa. In patients with small-focal pancreatic necrosis in the sterile phase of pancreatic necrosis, an average of  $1.8 \pm 0.3$  types of surgical interventions were performed. In large-focal pancreatic lesions, this value was  $2.2 \pm 1.2$ , and in subtotal pancreatic lesions -  $5.0 \pm 1.1$  stages of surgical intervention.

Cholecystectomy with bile duct drainage prevailed among patients with small-focal pancreatic necrosis in the sterile phase of the disease. Such a nature of surgical intervention is due to those cases when the operation was performed for acute calculous cholecystitis, but the intraoperative finding revealed small-focal pancreatic necrosis. In such cases, drainage of the bile ducts and drainage of the omental bursa were mandatory after cholecystectomy, followed by targeted conservative therapy of pancreatitis.

In the infected phase of pancreatic necrosis in patients with large-focal pancreatic lesions, an average of  $5.8 \pm 1.5$  surgical stages of surgery were performed per 1 patient,  $5.9 \pm 1.0$  in subtotal lesions, and  $6.6 \pm 2.1$  in total lesions.

As can be seen from the diagram, the variety of surgical techniques performed in the infected phase of pan-



creatic necrosis was more diverse than in the sterile phase.

The majority of patients (up to 82.3%) were operated on during the first week, while 45.9% of patients were operated on within the first 2 days from the onset of the disease, then in this group of patients the tactics of early operations in pancreatic necrosis was predominant.

One of the main factors that determines the severity of the course of pancreatic necrosis and the risk of a fatal outcome is the area of damage to the pancreas. Nevertheless, the division of patients according to the nature of pancreatic necrosis, that is, sterile or infected, is often somewhat conditional. This is due to the fact that the sterile form of pancreatic necrosis often transforms into an infected one.

The retrospective cohort study was based on data determining the final verification diagnosis. A number of patients during relaparotomy performed 2-3 weeks after the first operation had pathomorphological manifestations of an already infected form of pancreatic necrosis. In these patients, formed necrotic sequesters and abscesses of the omental bursa were found. Therefore, when analyzing, we took the final version of the diagnosis verification as a basis.

In total, relaparotomies were performed in 58 patients. At the same time, they were performed twice in 8 and three times in 4. In one patient, relaparotomy was performed 4 times.

In most cases, pancreatic necrosis proceeded with various complications, which were often combined and thus could manifest themselves in several variants and in the same patient. It is they who determine the urgency of surgical intervention and tactics for pancreatic necrosis.

Peritonitis was detected in 49 (55.5%) patients. Local peritonitis was diagnosed in 16.3% of patients, diffuse peritonitis in 22.4% and diffuse peritonitis in 61.2% of patients. The serous nature of the effusion was noted in 18.4% of patients, hemorrhagic - in 32.6%, purulent - in 14.3%, and fibrinopurulent - in 34.7% of patients.

Of course, it should be borne in mind that peritonitis in patients was an indication for surgery. However, taking into account the fact that minimally invasive interventions would have been very effective in case of serous or hemorrhagic exudate, nevertheless, at that time the main surgical technique was a more complex and traumatic laparotomy. And laparoscopy was performed only for diagnostic purposes and verification of the final diagnosis of the disease. At the same time, it was half of the deceased patients who had peritonitis. And here it

should be stated that peritonitis was one of the most common complications of pancreatic necrosis.

Cellulitis of the retroperitoneal space was in 2nd place (34.0%) after peritonitis. This type of complication of pancreatic necrosis was detected at various times from the onset of the disease, on average  $7.2 \pm 3.8$  days. Damage to the right half of the retroperitoneal space was noted in 24.2% of patients, the left half in 63.6% of patients, and total damage in 12.1% of patients. At the same time, in 28.9% of patients, lesions of the retroperitoneal space were determined only by infiltration without signs of suppuration at the time of intraoperative verification. However, after repeated surgery, 11.3% of patients were diagnosed with pancreatic abscesses.

The nature of complications characterizing the generalization of the purulent-inflammatory process in patients with different phases of the course of pancreatic necrosis was not ordinary.

Pancreatogenic sepsis in patients with the sterile phase of pancreatic necrosis (group I) was diagnosed in 39.5% of cases. Whereas among patients with the infected phase of pancreatic necrosis, it was diagnosed in 100% of cases. We would like to remind you that the third group of patients was formed at the expense of patients with severe sepsis and septic shock. Accordingly, the patients of the second group, who also had a generalized form of complications of the purulent-destructive process, were represented by the presence of sepsis syndrome or only by the syndrome of systemic inflammatory response of the body.

In 74 (76.3%) patients, pancreatogenic sepsis was diagnosed on the day of hospitalization. Of these, almost half of the patients (47.3%) were diagnosed with sepsis syndrome, represented by patients with an infected phase of pancreatic necrosis. Patients who formed the third study group (with the presence of severe sepsis and septic shock) (32.4%) had an exclusively infected form of pancreatic necrosis. At the same time, if there were 27.0% of patients with severe sepsis, then 5.4% of patients with septic shock.

Despite the ranking of patients with systemic inflammatory reaction syndrome by the presence of organ dysfunction or septic shock, nevertheless, the number of patients with sepsis syndrome on the day of hospitalization in the clinic turned out to be quite impressive (59.3%).

Systemic inflammatory reaction syndrome was diagnosed in the absence of a purulent focus and organ dysfunction in 20.3% of patients, and all of them were pre-

sented as patients with a sterile phase of pancreatic necrosis.

The distribution of patients depending on the number of signs of systemic inflammatory reaction syndrome showed that there were 4 clinical and laboratory signs (27.8%). The number of patients with 3 clinical and laboratory signs was only one patient behind. There were 21.6% of patients with 2 clinical and laboratory signs, and 23.7% of patients with 1 clinical and laboratory sign. It is the latter category of the nature of the manifestation of the systemic inflammatory reaction syndrome that was represented in more than half of patients with the sterile phase of pancreatic necrosis (60.5%).

It should be noted that the nature of the change in the numerical value curve of patients with the syndrome of systemic inflammatory reaction among patients with the sterile phase of pancreatic necrosis had an inverse correlation with the number of patients ( $R=-0.847$ ). In other words, as the number of clinical and laboratory signs of the systemic inflammatory response syndrome increased, there was a progressive decrease in the number of patients with pancreatic necrosis in the sterile phase. At the same time, among patients with the infected phase of pancreatic necrosis, the correlation significance between the number of clinical and laboratory signs of the systemic inflammatory response syndrome and the number of patients had a close direct correlation ( $R=0.954$ ).

According to the records of the patient's medical history, the presence of pancreatogenic sepsis was recorded 405 times. On average, each patient had 5.5 times. Such a high value of sepsis registration was probably due to the amount imposed on the deceased patients. However, when subtracting the lethal outcomes among patients with pancreatogenic sepsis, this indicator decreased by only 0.4 times. The ratio between patients with the sterile phase of pancreatic necrosis and those with infected patients was 2.1 times in favor of the latter.

The mortality rate of patients with acute pancreatic necrosis was 30.9% (30 cases) and was distributed as follows in the dynamics of treatment.

On the day of admission, 1 (3.3%) patient died, by the end of the first day – another 1 (3.3%) patient. Subsequently, 2 (6.7%) patients died on days 2-3 of treatment, 7 (23.3%) patients died on days 3-7, 10 (33.3%) patients died on days 7-14, and 9 (29.9%) patients died in the long term (over 14 days and up to 3 months). In general, 83.3% of patients died in the subgroup with acute infected pancreatic necrosis, and the remaining 16.7% - with acute sterile pancreatic necrosis.

Thus, the first 14 days were the most dangerous, during which 21 (70.1%) patients out of 30 died. When comparing the total amount of complications for different systems in the deceased, it was found that on average for each lethal outcome on days 1-7 there were 5.6-6.5 complications, and on days 7-14 there were 4.9-6.6 complications associated with organ dysfunction. Of these, 4.5 – 5.8 complications on days 1-7 of admission were associated with disorders of vital organs.

A combination of severe disorders of vital organs occurred in almost all patients who died in the first 3 days of observation – 3.6-3.8 such disorders per 1 patient, and later this indicator decreased slightly.

The decrease in the frequency of septic shock in the first 3 days fully corresponds to the number of dead patients, which is associated with the initial severity of admitted patients. Starting from day 3, there was a persistence of cases of septic shock due to the deterioration of the patient's condition, inadequate treatment in the development of complications (first of all, purulent-septic).

The most common causes of death were generalization of infection (70.9%), peritonitis (59.6%), cardiovascular disorders (58.3%) and hepatic-renal disorders (45.4%) and other complications. Arrosive bleeding was less common (6.7%). Such a high percentage of multi-organ "interest" prompted us to retrospectively study pathomorphological changes in patients with a comparative analysis of lethal outcomes.

In 30 (30.9%) of the deceased, the data of pathomorphological examination of organs were studied. At the same time, it was found that fatty and granular dystrophy of liver cells was observed in 29 (96.7%) cases, cirrhosis of the liver – in 9 (30.0%), amyloidosis – in 4 (13.3%). Renal changes in 23 (76.7%) of the deceased were characterized by granular dystrophy of the epithelium of the convoluted tubules and in 2 (6.7%) – by amyloidosis. Pathological changes in the heart muscle were found in 25 (83.3%) patients (no changes were found in 16.7%). These changes were characterized by granular dystrophy, combined in three patients with fragmentation of muscle fibers.

## CONCLUSION

Thus, the analysis of the registration of the presence or absence of pancreatogenic sepsis at the time of hospitalization of patients revealed that pancreatic necrosis in the infected phase is characterized by a predominance of sepsis without impairment of the function of vital organs (more than half of the patients). At the same time, among patients with the sterile phase of pancreatic necrosis, this type of inflammatory complication manifested itself only

in 1/3 of patients without impairment of the function of vital organs. However, in the dynamics of the treatment, the picture regarding the manifestation of the development of the generalization of the inflammatory process has changed radically.

The high mortality rate among patients in whom repeated relaparotomies were performed indicates that it is necessary to postpone their performance in infected pancreatic necrosis. They are acceptable when they are performed in conditions of process delimitation. The delimited necrosis of the pancreas is lysed and sequestered. In such cases, the sanitizing and draining goal of surgical intervention is easily achievable. This is what allows you to perform surgery in a more favorable background, as it will be less traumatic.

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