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Immediate and Long-Term Results of Complex Traditional Treatment of Patients with Pancreatic Necrosis Complicated by Sepsis

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ABSTRACT

Background. An analysis of the literature over the past 10 years has shown that there are more and more supporters of conservative therapy of pancreatic necrosis with active wait-and-see tactics. To improve the effectiveness of treatment and diagnostic tactics, proponents of this approach offer complexes of algorithms.

Material. A retrospective cohort study of the results of a comprehensive examination and treatment of 97 patients with pancreatic necrosis was conducted. All patients were treated and examined in the Bukhara regional branch of the Republican Scientific and Practical Medical Center for Emergency Medical Care from 2013 to 2017.

Conclusion. And the results of traditional methods of treatment of pancreatic necrosis complicated by sepsis showed the presence of a high level of complications of the disease (38.1%) and mortality (30.9%), due to the lack of objective criteria for predicting the development of pancreatogenic sepsis and multiple organ dysfunction syndrome, which requires detailed studies of the pathogenetic mechanisms of this formidable disease.

Keywords: Pancreatic necrosis, systemic inflammatory response syndrome, sepsis as a complication of pancreatic necrosis, conservative treatment, surgical treatment, immediate and long-term results

INTRODUCTION

There are many factors that determine the choice of treatment for pancreatic necrosis, among them the most significant is the speed and area of development of the necrobiotic process, both in the pancreas itself and around it. [1, 2, 6, 9]

Meanwhile, one of the priority approaches to date in choosing tactics for the treatment of pancreatic necrosis is to consider the phases of the inflammatory process. Based on this approach, the following principles of choosing treatment tactics have taken root in modern pancreatology: to use of purely conservative therapy as a

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priority; conservative therapy with active expectant tactics and the use of a surgical method of treatment according to strict indications (uncertainty in diagnosis, the presence of progressive peritonitis and/or shock, progressive jaundice); actively use the surgical method of treatment, considering conservative therapy only a period of preoperative preparation. [3, 10, 29, 30]

An analysis of the literature over the past 10 years has shown that there are more and more supporters of conservative therapy of pancreatic necrosis with active wait-and-see tactics. To improve the effectiveness of treatment and diagnostic tactics, supporters of this approach offer complexes of algorithms, which are based on: the fight against pain and problems of bile outflow; suppression of the secretory activity of both the pancreas itself and the stomach; complex anti-enzyme, anti-inflammatory and detoxification therapy; prevention of infection of the pancreas and correction of vascular changes in this organ. [1-3, 6, 7, 9, 10, 13, 14, 29]

The basis of the leitmotif of the surgical method of treating pancreatic necrosis is the prevention of the death of the patient. Proponents of active wait-and-see tactics, using the entire available arsenal of conservative therapy, begin to use surgical techniques in patients with pancreatic necrosis with only one goal - to prevent further rapid progression of pancreatic necrosis. In this regard, many issues related to the indications and timing of surgical interventions in patients with pancreatic necrosis remain far from being resolved and sometimes even controversial. [4, 6-9]

An absolute indication for the surgical method of treating pancreatic necrosis is its purulent-necrotic complication. On this issue, most surgeons are of the same opinion. However, in the matter of surgical treatment of sterile pancreatic necrosis, many aspects related to the timing and scope of surgical intervention are still fragmented. And this is one of the main issues that are discussed at specialized conferences and congresses on pancreatology. Do I need surgery for the sterile form of pancreatic necrosis?

Such complications of the disease as infection, abscessing, and biliary pancreatic necrosis that is not amenable to endoscopic intervention are considered generally recognized direct indications for the use of surgical methods of treatment. However, the variants of complications of pancreatic necrosis in the form of progressive deterioration of the patient's condition, the development of multiple organ failure, progressive necrosis of the pancreas, as well as its total defeat with focal infection, remain controversial. [11]

Other authors prioritize general changes in the body and believe that direct indications for surgical methods of treatment should be in the form of the presence of purulent peritonitis, progressive multiple organ failure syndrome, not the effectiveness of conservative therapy, and even the possible development of sepsis syndrome. [12]

But there is also a group of third opinions when the indications for surgical methods of treatment should be individual cases that go beyond the general rules of restriction. As an example, we can cite the opinion of researchers regarding the indications for surgery in the development of the clinical picture of peritonitis, even under the condition of only infiltrative changes in the pancreas. [31]

Such versatility of modern information prompted us to conduct a study to assess the immediate and long-term results of complex traditional treatment of patients with pancreatic necrosis complicated by sepsis.

MATERIAL AND METHODS

A retrospective cohort study of the results of a comprehensive examination and treatment of 97 patients with pancreatic necrosis was carried out. All patients were treated and examined in the Bukhara regional branch of the Republican Scientific and Practical Medical Center for Emergency Medical Care from 2013 to 2017.

In 38 (39.18%) cases, pancreatic necrosis was pregnant, 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 subgroups: subgroup I – patients with sterile pancreatic necrosis (38 patients; 39.18%), subgroup II – patients with infected pancreatic necrosis (35 patients; 36.08%), subgroup III – 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. The base contingent accounted for patients of the most able-bodied mature age (Figure-1).

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

The treatment of patients in the clinic since the onset of the disease was not unambiguous but differed in a certain pattern among the subgroups. In the group of pa-

tients, active surgical tactics were predominantly used, consisting in conducting early laparotomies, 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 the ongoing conservative therapy and/or the presence of signs of peritonitis.

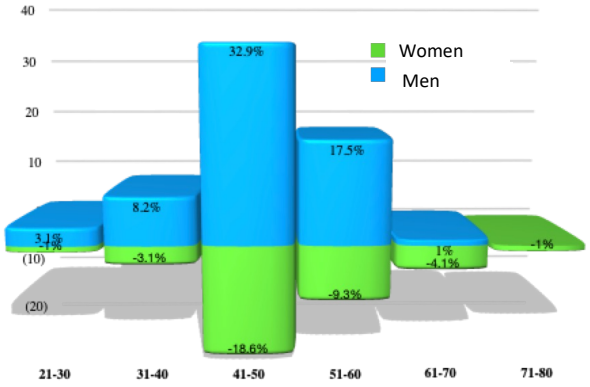

Figure-1. The nature of the distribution of patients by sex and age

If laparotomy was performed during the sterile phase of pancreatic necrosis, at the first stage, the abdominal organs were revised. If pancreatic necrosis was suspected, the omentum bag was opened, and a visual audit was performed. The operation was completed by sanitation and drainage of the omentum bag and abdominal cavity with several drains. In the case of a dead 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 the timely and complete performance of necrsequestrectomy and drainage of purulent cavities of parapancreatic tissue for subsequent sanitation. They opened the omentum bag, all possibly forming cavities that are 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 performed in the retroperitoneal space, omentum bag, and abdominal cavity.

Assessment of the condition of a patient with acute infected pancreatic necrosis complicated by sepsis, a gradation scale consisting of the following criteria was used: dynamics and frequency of development of multiple organ dysfunction syndrome; frequency and severity of purulent complications in the overall structure of therapeutic measures.

The immediate results of treatment of patients with pancreatic necrosis were evaluated according to four standard groups of results: excellent, good, satisfactory, and unsatisfactory. The excellent result was characterized by the preservation of the anatomical integrity and functional usefulness of the pancreas against the background of the absence of any inflammatory phenomena. A good result was characterized by a violation of the anatomical integrity of the pancreas in the presence of its compensated functional activity, which does not require medical correction. There are no inflammatory phenomena. A satisfactory result was characterized by a violation of the anatomical integrity of the pancreas, and the presence of local complications that do not require special surgical interventions and tend to heal or scar on their own soon. The functional activity of the pancreas is preserved or compensated by medication. Temporary local inflammatory phenomena associated with the course of the above complications are possible. The unsatisfactory result was characterized by a violation of the anatomical integrity of the pancreas. The presence of local complications requiring repeated surgical interventions, the presence of arrosive bleeding requiring special intervention. The functional activity of the pancreas is impaired without the prospect of recovery. Prolonged drug compensatory (substitution) therapy is required. Inflammatory phenomena associated with ongoing necrosis of the pancreatic parenchyma persist but with a tendency to restrict.

The death of the patient as a criterion for the result of treatment could be classified as unsatisfactory, however, given the high frequency of this outcome of treatment of patients with pancreatic necrosis, this item is highlighted separately.

To study the long-term results of treatment and the quality of life of patients who underwent pancreatic necrosis, the following methods were used: a questionnaire using the GIQLI questionnaire [5], clinical examination, ultrasound and computed tomography of the abdominal organs, and magnetic resonance imaging.

The data obtained in the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2016 software package, including the use of built-in aggregation functions and BioStat for Windows. The methods of variational parametric and nonparametric statistics were used. The level of significance $p<0.05$ was taken as statistically significant changes.

RESULTS

According to archival data, acute pancreatitis was found only in 68 (71.1%) patients. In other cases (28.9%), before hospitalization in our clinic, diagnoses of acute cholecystitis (15.5%), perforation of gastroduodenal ulcer (7.2%), acute intestinal obstruction (4.1%) and acute appendicitis (3.1%) were established.

In the medical history at the time of hospitalization of patients, 687 pathological signs were described. Of these, 26.6% accounted for patients of Subgroup I, 39.7% for patients of subgroup II and 33.6% for patients of subgroup III.

The distribution of these pathological signs showed that the pain syndrome was prevalent (it was noted in all 100% of cases). The 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, and between the shoulder blades. The pain was the flagship among the pathological manifestations of the disease in all analyzed subgroups.

Dyspeptic disorders are a constant companion of destructive pancreatitis. They were in second place in terms of frequency of registration after pain syndrome and accounted for 93.8%. Among the varieties of dyspeptic disorders, nausea, uncontrollable vomiting that does not bring relief, constipation, flatulence and bloating prevailed. At the same time, in subgroups II and III, this symptom complex was observed in all patients, while in patients of subgroup I 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 subgroups II and III, whereas among patients of subgroup I they occurred only in 29 (76.3%) patients.

Almost half of the patients with destructive pancreatitis (43.3%) had icteric sclera and skin at admission. There were 34.2% of patients in Subgroup I, 40.0% of cases among patients in Subgroup II and in 62.5% of cases among patients in Subgroup III.

Pathological signs from the cardiovascular system were in the form of tachycardia, registered in 90.7% of cases and a decrease in systolic blood pressure below 100 mm Hg. Art. in 68.0% of patients. Tachycardia in 100% of cases was recorded among patients of subgroups II and III, while in patients of subgroup I, increased heart rate was recorded 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 0C was recorded in 75 (77.3%) cases. At the same time, among patients of subgroups II and III, as in the previous case, hyperthermia was noted in all cases, while in patients of subgroup I only in 16 (42.1%) cases.

Disorders of the respiratory system were noted in 70 (72.2%) patients. In the first subgroup of patients with dyspnea, there were 36.8%, in the second subgroup – 91.4%, and in the third subgroup –100% of cases.

The identified pathological manifestations of the genitourinary system were presented in the form of hematuria, proteinuria, cylindruria, or a combination thereof. In general, there were 37 (38.1%) patients with such disorders. There was only one patient in Subgroup I, 12 (34.3%) patients in Subgroup II, and all 24 patients in Subgroup III.

Disorders of the psyche and nervous system at admission were detected in 33 (34.0%) patients. They manifested themselves in 22 (22.7%) patients in the form of euphoria, anxiety and negativism. Psychomotor agitation and hallucinations were diagnosed in 9 (9.3%) patients. A sharp depression of the psyche, sometimes up to a coma, was diagnosed in 2 (2.1%) patients.

Diagnostic laparoscopy was performed in 48 (49.5%) patients. On the 1st day of hospitalization, it was used in 19 patients, on the 2nd day – in 10 patients, on the 3rd day – in 8 patients, on the 4th day – in 7 patients and on the 5th day – in 4 patients. The average duration of this intervention was 3.1±1.1 days.

Clinical and morphological parallels revealed the predominance of patients with total (32.0%) and subtotal (26.8%) necrotic lesions of the pancreas (Figure-2). In subtotal lesions, the predominant lesion was 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) prevailed, and in the second case, common (46.6 times) necrotic lesions of the pancreas.

The average severity of acute pancreatic necrosis was 8.4±1.1 points (Figure-3).

The variance of the mean value was distributed downward from 10.1±0.9 points in total pancreatic necrosis to 6.8±2.9 points in small-focal pancreatic necrosis ($p<0.05$). In the infected form of pancreatic

necrosis, the severity index of the lesion was 1.9±0.3 points greater than in patients with a sterile form of pancreatic necrosis (p<0.05).

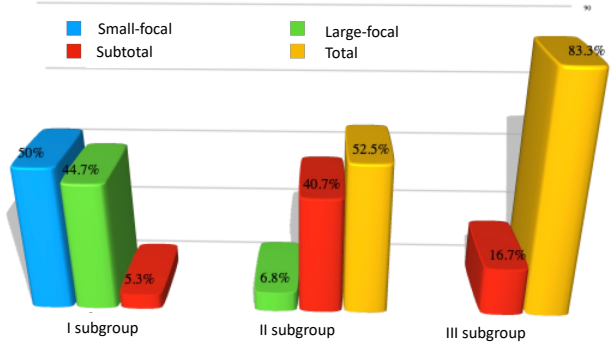

Figure-2.
The nature of the correlation of clinical and morphological parallels

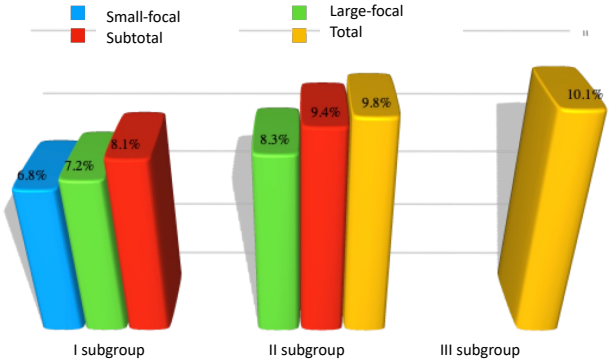

Figure-3.
The nature of the ratio of the severity of pancreatic necrosis lesions

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±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 omentum bag 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 bag. But the drainage of the stuffing box was carried out repeatedly, which causes the difference in values.

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

Interventions for cholelithiasis were reduced to cholecystostomy (1.3%) and cholecystectomy with bile duct drainage (8.2%).

In 22 (4.9%) cases, autopsy and drainage of a suppurating pancreatic cyst were performed.

The volume and nature of the performed surgical interventions in the section of the pancreatic necrosis phase showed a prevalence of 4.4 times in patients with infected pancreatic necrosis. In the phase of sterile pancreatic necrosis, an average of 2.2±1.0 surgical interventions were performed per patient, and in the infection phase, 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 distributed evenly between abdominal drainage, drainage of the omentum bag, cholecystostomy, cholecystectomy with ductal drainage and omentobursostomy with marsupialization of the omentum bag. In patients with small-focal necrosis of the pancreas in the sterile phase of pancreatic necrosis, an average of 1.8±0.3 types of surgical interventions were performed. In large-focal cases, this value was 2.2±1.2, and in subtotal pancreatic lesions, 5.0±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. This nature of the surgical intervention is due to those cases when the operation was performed for acute calculous cholecystitis, but intraoperative finding revealed small-focal pancreatic necrosis. In such cases, after cholecystectomy, drainage of the bile ducts and drainage of the omentum bag was performed, followed by targeted conservative therapy for pancreatitis.

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

The type of surgical techniques performed in the infected phase of pancreatic necrosis was more diverse than in the sterile phase. Most 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 for pancreatic necrosis were predominant.

A retrospective cohort study was based on data that determine the final verification diagnosis. A few patients during the 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 sequestrations and abscesses of the omentum bag were found. Therefore, in the analysis, we took as a basis the final version of the diagnosis verification.

A total of 58 patients underwent relaparotomy. At the same time, 8 of them were performed twice, and 4 - three times. In one patient, a 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 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 serious nature of the effusion was noted in 18.4% of patients, hemorrhagic in 32.6%, purulent in 14.3% and fibrinous-purulent in 34.7% of patients.

Of course, it should be borne in mind that peritonitis in patients was an indication for surgical intervention. However, given the fact that with the serous or hemorrhagic nature of the exudate, minimally invasive interventions would be very effective, nevertheless, at that time of medical care, the main surgical technique remained 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 frequent complications of pancreatic necrosis.

Postretroperitoneal phlegmon was in 2nd place (34.0%) after peritonitis. This type of complication of pancreatic necrosis was detected at different times from the onset of the disease, on average, 7.2±3.8 days. The lesion of the right half of the retroperitoneal space was noted by us in 24.2% of patients, the left half in 63.6% of patients and the total 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, with repeated surgery, 11.3% of patients were diagnosed with pancreatic abscesses.

The nature of the complications characterizing the generalization of the purulent-inflammatory process in patients with different phases of pancreatic necrosis was not ordinary (Table-1).

Table-1. The nature of the frequency of registration of the generalization of the inflammatory process

TYPE OF PROCESS	PHASES OF PANCREATIC NECROSIS			
	Sterile		Infected	
	n	%	n	%
Systemic inflammatory response syndrome	15	100	0	0
Sepsis syndrome	0	0	35	59,3
Severe sepsis	0	0	20	33,9
Septic shock	0	0	4	6,8

Pancreatogenic sepsis in patients with a sterile phase of pancreatic necrosis (Subgroup 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. I would like to remind you that the III subgroup of patients was formed at the expense of patients with severe sepsis and septic shock. Accordingly, patients II Subgroups, which also had a generalized form of complication of the purulent-destructive process, were represented by the presence of sepsis syndrome or only by the syndrome of the 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 III study subgroup (with the presence of severe sepsis and septic shock), who accounted for 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 response syndrome by the presence of organ dysfunction or septic shock, nevertheless, patients with sepsis syndrome on the day of hospitalization in the clinic turned out to be quite an impressive number (59.3%).

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

resented by patients with a sterile phase of pancreatic necrosis (Table-2).

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

Table-2. Distribution of patients by the number of signs of systemic inflammatory response syndrome

NUMBER OF SIGNS OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME	PHASES OF PANCREATIC NECROSIS			
	Sterile		Infected	
	n	%	n	%
SIRS0-1	23	60,5	0	0
SIRS2	7	18,4	14	23,7
SIRS3	5	13,2	21	35,6
SIRS4	3	7,9	24	40,7

It should be noted that the nature of the change in the curve of the numerical value of patients with systemic inflammatory reaction syndrome 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 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 within the infected phase of pancreatic necrosis, the correlation significance between the number of clinical and laboratory signs of systemic inflammatory response syndrome and the number of patients had a close direct correlation (R = 0.954).

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 the predominance of sepsis without dysfunction of vital organs (more than half of the patients). At the same time, among patients with a sterile phase of pancreatic necrosis, this type of inflammatory complication was manifested only in 1/3 of patients without dysfunction 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.

As can be seen from the diagram, the curve of changes in the frequency of registration of pancreatogenic sepsis in dynamics during 2 weeks of treatment only increased (Figure-4).

According to the records of the medical history, the presence of pancreatogenic sepsis was recorded 405 times. On average, each patient accounted for 5.5 times. Such a high value of sepsis registration was probably due to the amount imposed on the deceased patients. However, when subtracting deaths among patients with pancreatogenic sepsis, this figure decreased by only 0.4 times. The ratio between patients with a sterile phase of pancreatic necrosis and with an infected one was 2.1 times in favor of the latter (Figure-5).

Mortality among patients with acute pancreatic necrosis was 30.9% (30 cases) and the dynamics of treatment was distributed as follows (Figure-6).

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 2-3 days of treatment, 7 (23.3%) patients died on days 3-7, 10 (33.3%) patients died on days 7-14 and another 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.

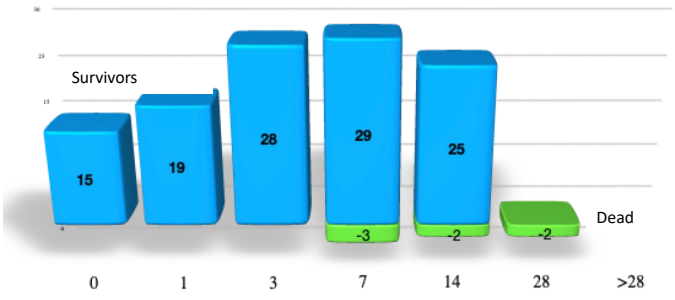

Figure-4. Comparative characteristics of the dynamics of surviving and deceased patients complicated by sepsis in the sterile phase of pancreatic necrosis.

Thus, the first 14 days turned out to be the most dangerous, during which 21 (70.1%) out of 30 patients died. When comparing the total amount of complications for

various systems in the victims, it was found that, on average, there were 5.6-6.5 complications for each death on days 1-7, and 4.9-6.6 complications associated with organ dysfunction on days 7-14. Of these, 4.5 – 5.8 complications on days 1-7 of admission of patients were associated with impaired activity of vital organs.

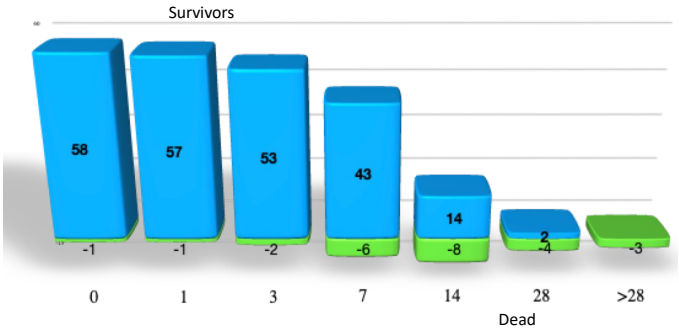

Figure-5. Comparative characteristics of the dynamics of surviving and deceased patients complicated by sepsis in the infected phase of pancreatic necrosis.

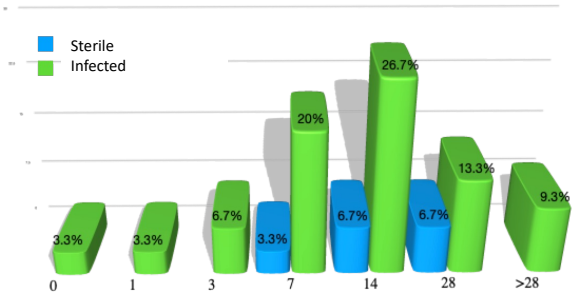

Figure-6. Mortality rate

The 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 figure decreased slightly.

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

The most common causes of death in pancreatic necrosis were generalization of infection (70.9%), peritonitis (59.6%), cardiovascular disorders (58.3%) and hepatorenal disorders (45.4%) and other complications. Arrosive bleeding was less common (6.7%). Such a high percentage of multiple 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 degeneration of liver cells was observed in 29 (96.7%) cases, cirrhosis of the liver – in 9 (30.0%), and amyloidosis – in 4 (13.3%). Kidney 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%) –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 the fragmentation of muscle fibers. Of the internal organs, the liver underwent the most profound changes, which, as is known, is exposed to purulent intoxication to a greater extent than other organs. The revealed changes were characterized by granular dystrophy of internal organs, combined in one patient with damage to several organs at once and the development of multiple organ failures.

Thus, the high mortality rate among patients who have undergone repeated relaparotomies indicates that it is necessary to delay their implementation in infected pancreatic necrosis. They are acceptable when they are performed in conditions of delimitation of processes. Delimited necrosis of the pancreas is lysed and sequestered. In such cases, the sanitizing and draining goal of surgery is easily achievable. This is what allows you to perform surgery in a more favourable background, as it will be less traumatic.

The results of the treatment of patients were evaluated according to the scale improved by us according to the gradations of excellent, good, satisfactory and unsatisfactory (Table-3).

Of the 97 patients, 3 (3.1%) achieved complete preservation of the anatomical integrity and functional activity of the pancreas according to the results of treatment.

Good results of treatment, in the form of a violation of the anatomical integrity of the pancreas, but in the presence of compensated functional activity, which does not require medical correction, were found in 15 (15.5%) patients. All of them were without any inflammatory phenomena. Among such patients, there were often cases with incorrect diagnoses. Among patients with a sterile form of pancreatic necrosis, this indicator exceeded that of patients with an infected form of pancreatic necrosis by 3.1 times.

The results of treatment, which ended with a violation of the anatomical integrity of the pancreas (10 patients), the presence of local complications that did not require special surgical interventions with a tendency to self-healing or scarring soon, were achieved in 12 (12.4%) patients.

Table-3. Immediate results of treatment of patients with pancreatic necrosis

RESULTS	PHASES OF PANCREATIC NECROSIS			
	Sterile		Infected	
	n	%	n	%
Great	3	7,9	0	0
Good	10	26,3	5	8,5
Satisfactory	6	15,8	6	10,2
Unsatisfactory	14	36,8	23	39,0
Lethality	5	13,2	25	42,4

In 7 (7.2%) patients, the functional activity of the pancreas was preserved, but in 5 (5.2%) patients it was compensated by medication. In 3 (3.1%) patients, there were temporary local inflammatory phenomena associated with the course of the above complications. In general, this result of treatment was higher by 5.6% among patients with a sterile form of pancreatic necrosis than among patients with an infected form of pancreatic necrosis.

In 15 (15.4%) patients, the anatomical integrity of the pancreas was impaired. At the same time, 12 (80.0%) of them had local complications that required repeated surgical interventions. In 1 (1.03%) patient, the probability of developing arrosive bleeding remained, which was stopped by repeated endoscopic interventions. The functional activity of the pancreas was impaired in 22 (22.7%) patients without the prospect of recovery. All of them acquired diabetes mellitus. Prolonged drug compensatory (substitution) therapy was necessary for 18 (18.6%) patients. In 3 (3.1%) patients, inflammatory phenomena associated with ongoing necrosis of the pancreatic parenchyma persisted, but all of them tended to restrict. This treatment outcome was higher among patients with an infected form of pancreatic necrosis by 2.2%.

The average bed days of the total number of patients was 49.1±9.2 bed days (Table-4).

It should be borne in mind that among patients with a sterile form of pancreatic necrosis, there was no total damage to the pancreas, and among patients with an infected form of pancreatic necrosis there was no small-focal lesion. In this regard, the average value of bed days in patients with small-focal pancreatic necrosis was 38.4±4.2 bed days, while among patients with total pancreatic necrosis, it was 1.7 times more.

The average number of bed days among patients with sterile pancreatic necrosis was 42.9±3.5 bed days, and with the infected form, patients were treated for 12.5 days longer.

The analysis of bed days among patients without considering deceased patients changed the picture of values in favour of an increase in terms (Table-5). For example, the average value of bed days in this statistical analysis was 7.6±2.1 bed days more than in the general cohort of patients.

Table-4. Number of bed days from the total cohort of patients with pancreatic necrosis

THE SCOPE OF THE LESION	PHASES OF PANCREATIC NECROSIS			
	Sterile		Infected	
	n	%	n	%
Small-focal	38,4	4,3	0	0
Large-focal	41,9	3,9	43,1	4,8
Subtotal	48,4	3,1	59,3	5,2
Total	0	0	63,9	4,1

The increase in the inpatient period of treatment of patients in the second cohort (excluding deceased patients) was higher in all gradations than in the first cohort (total number of patients). However, this increase was not proportional. For example, in the case of patients with small-focal sterile pancreatic necrosis in the second cohort, the duration of bed-days was longer by only 1 bed-day, while the comparative analysis between the first and second cohorts, as well as small-focal and total pancreatic lesions was 2 times longer (38.4±4.3 and 78.9±5.8 bed-days, respectively; $p<0,05$).

Long-term results were evaluated in 63 patients who underwent pancreatic necrosis. At the same time, in a hospital, long-term results were evaluated in 118 patients.

Table-5. Number of bed days from the total cohort of patients with pancreatic necrosis, excluding deaths

THE SCOPE OF THE LESION	PHASES OF PANCREATIC NECROSIS			
	Sterile		Infected	
	n	%	n	%
Small-focal	39,6	6,3	0	0
Large-focal	45,9	8,3	51,9	2,8
Subtotal	49,9	4,2	73,5	4,2
Total	0	0	78,9	6,3

A survey of patients showed that the average point gradation on the GIQLI scale was 117.9±2.2 points. The division of the structure of the point gradation was carried out depending on the subgroups of patients according to the direct results of treatment. Thus, of the total value, the maximum (136.9±1.9 points) was in patients with excellent immediate treatment results. In the remaining patients, a decrease in the mean score had a direct correlation with the immediate results of treatment. For example, the minimum score (105.6±0.8 points) was in patients with unsatisfactory immediate treatment results.

The analysis of the quality-of-life indices of patients depending on the transferred form of pancreatic necrosis also had a significant difference ($p<0.001$). In patients with the sterile phase of pancreatic necrosis, the average value of the GIQLI score was 121.2±1.2 points, than among patients who underwent the infected form – 107.1±2.1 points ($p<0.001$).

Recurrence of acute pancreatitis was noted in 11 (33.3%) of 33 patients who underwent aseptic destructive complications, and in 9 (26.5%) of 34 patients who underwent infected destructive complications. The main reasons for the development of recurrent pancreatitis were factors such as alcohol intake (25.0%) and excessive consumption of fatty (25.0%) and fried foods (50.0%).

The assessment of the functional insufficiency of the pancreas in the long-term period was checked by the level of elastase-1 concentration in the feces. The normal value was at the level of elastase-1 in the feces above 200 mg in 1 g of feces.

In patients who underwent a sterile form of pancreatic necrosis in half of the cases (51.2%), a normal value of this indicator in the feces was revealed. A moderate variant of enzymatic deficiency was detected in 45.2% of patients, and in 3.6% of cases, a severe form of exocrine insufficiency was diagnosed.

In patients who underwent an infected form of pancreatic necrosis in half of the cases (28.3%), a normal value of this indicator in the feces was revealed. A moderate variant of enzymatic deficiency was detected in 66.9% of patients, and in 4.8% of cases, a deficiency of elastase-1 activity in the contents of feces was diagnosed, which corresponded to a severe form of exocrine insufficiency.

Diabetes mellitus developed in 32.9% of patients. At the same time, type I diabetes mellitus was diagnosed in 12 cases, and type II was diagnosed in 15 cases.

Incisional ventral hernia developed in 23 patients. In addition, among the morphological changes in the pancreas in the long-term period of the postoperative period, pancreatic pseudocysts were detected in 12.8% of cases.

Thus, the analysis of the long-term results of treatment of patients with pancreatic necrosis showed an excess of negative values among patients who underwent an infected form of pancreatic lesions. All this allows us to conclude that when choosing the optimal treatment tactics for pancreatic necrosis, one should focus not only on the patient's condition and the course of the disease, but also consider the possible decrease in the quality of life or the development of complications at a later date.

DISCUSSION

Unfortunately, even intensive complex treatment using active surgical tactics was not able to provide positive treatment results. At the same time, maintaining a high level of complication of pancreatic necrosis is accompanied by a violation of the natural mechanisms of the regressive course of the purulent-necrotic process. An example is the high level of septic complications identified by us as a result of a retrospective analysis of patients with pancreatic necrosis [15].

As shown by the presented clinical cases, the performance of early laparotomies against the background of ineffective conservative therapy, in most cases, does not allow to solve the problem in a positive way. In such cases, pancreatic necrosis did not stop, which, accordingly, ended with the progression of sepsis, multiple organ

failure and death. In such cases, the operation acquired a very traumatic character, aggravating the already critical condition of the patient. This indicates the need for a radical revision of active surgical tactics in pancreatic necrosis, especially in its sterile form. We also believe that it is advisable to introduce new minimally invasive technologies, since the use of traditional methods of surgical treatment of pancreatic necrosis against the background of a serious condition of patients initially predetermines high mortality. However, questions related to objective criteria for choosing a method of surgical intervention or conservative treatment should not be based only on morphostructural changes in the pancreas [28].

As mentioned above, underestimation of the severity of the patient's condition, even with the use of modern diagnostic methods, as well as the use of screening methods in the assessment of septic complications, contributed to the progression of the purulent-inflammatory process with the involvement of more and more new areas of the pancreas and more and more intensive involvement of vital organs in the process. At the same time, the initial state of the body becomes important. In the presence of concomitant diseases of internal organs (diabetes mellitus, cirrhosis of the liver, etc.), this process is inevitable. The basis for such an assumption can be the given numerical data [27].

The main causes of mortality during the disease are disorders of vital organs. In subsequent terms, along with mortality due to the initially serious condition of patients, liver disorders begin to come to the fore, while maintaining a high frequency of generalization of infection. An increase in the high frequency of purulent-septic complications during the disease, especially their most severe types – severe sepsis and septic shock, leads to changes in thanatogenesis with the dominance of this group of complications [16].

A very significant circumstance in the cause of death of patients is the frequent combination of disorders of the activity of 2-3 or more vital organs and systems (multiple organ failure syndrome), especially pronounced during the height of the disease [26].

The presented data, on the one hand, confirm the well-known scheme of the course of acute pancreatic necrosis: the inflammatory process in the pancreas with the enzymatic breakdown of the parenchyma leads to the development of systemic inflammatory reaction syndrome, which is a response of the macroorganism to the ongoing process of endotoxicosis. In patients with infected pancreatic necrosis, this process is aggravated due to bacterial invasion and uncontrolled cytokine discharge into the systemic circulation. All this leads to a progressive disruption of the microvasculature, which, under conditions of enzymatic destruction of the pancreas, may take the form of the initial stage of a vicious circle, the exit from which becomes impossible by performing active surgical intervention in the early stages of the disease [18].

Infection in the pancreas and breakthrough of the capillary barrier leads, together with toxins and microbes, to an increase in the functional load on vital organs with the development of their multiple organ failure and subsequent generalization of the pathological process with the development of septic shock [25].

On the other hand, a certain relationship between the pathomorphological structural transformations of the pancreas and vital organs amid the disease may indicate an increasing endothelial interdependence between these organs in this disease. This pathological process is known today as endothelial dysfunction [19].

At first glance, it is enough to understand that the endothelial system functionally regulates not only local processes but also systemic ones. Unfortunately, this is not enough to prove the mandatory presence of such relationships in patients with sterile and infected forms of pancreatic necrosis. It is required to conduct targeted additional studies with an accurate assessment of the state of the endothelial system under normal conditions, and then in the dynamics of the development of pancreatic necrosis. Moreover, an important aspect of such a study is the assessment of the endothelial system in various variants of inflammatory lesions of the pancreas (acute pancreatitis, sterile pancreatic necrosis, infected pancreatic necrosis, and infected pancreatic necrosis complicated by sepsis).

To answer these questions, it is necessary to significantly expand the arsenal of test studies, as well as to solve several methodological problems. The complexity and certain risk of performing these methods in the clinic prompted us to tackle this problem first in an experiment. We will inform you about the results of these experimental studies in our subsequent publications.

CONCLUSION

Thus, the analysis of the results of traditional methods of treatment of pancreatic necrosis complicated by sepsis showed the presence of a high level of complications of the disease (38.1%) and mortality (30.9%), due to the lack of objective criteria for pre-

dicting the development of pancreatogenic sepsis and multiple organ dysfunction syndrome, which requires detailed studies of the pathogenetic mechanisms of this formidable disease.

Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The author agrees to open the publication.

Availability of data and material – Available.

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SEPSIS BILAN ASORATLANGAN PANKREONEKROZI BILAN BEMORLARNI KOMPLEKS AN'ANAVIY DAVOLASHNING YAQIN VA UZOQ MUDDATLI NATIJALARI

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ABSTRAKT

Dolzarbligi. So'nggi 10 yil mobaynida adabiyotlar tahlili shuni ko'rsatdiki, faol kutish taktikasi bilan oshqozon nekrozining konservativ terapiyasi tarafdorlari tobora ko'payib bormoqda. Davolash va diagnostika taktikasi samaradorligini oshirish uchun ushbu yondashuv tarafdorlari algoritmlarning komplekslarini taklif qilishdi.

Material. Oshqozon nekroziga chalingan 97 nafar bemorni kompleks tekshirish va davolash natijalarini retrospektiv kogort o'rganish o'tkazildi. 2013-2017 yillarda Respublika shoshilinch tibbiy yordam ilmiy-amaliy tibbiyot markazi Buxoro viloyat filialida barcha bemorlar davolanib, tekshirildi.

Xulosa. Sepsis bilan asoratlangan oshqozon nekrozini davolashning an'anaviy usullari natijalari kasallikning yuqori darajadagi asoratlari mavjudligini (38,1%) va o'lim (30,9%), pankreatogen sepsis va ko'p a'zolar disfunksiyon sindromi rivojlanishini bashorat qilishning ob'ektiv mezonlari yo'qligi sababli, ushbu qo'rqinchli kasallikning patogenetik mexanizmlarini batafsil o'rganishni talab qiladi.

Tayanch iboralar: Oshqozon osti bezi nekrozi, tizimli yallig'lanishga javob berish sindromi, sepsis oshqozon nekrozining asoratlari sifatida, konservativ davolash, jarrohlik davolash, yaqin va uzoq muddatli natijalar

НЕПОСРЕДСТВЕННЫЕ И ОТДАЛЁННЫЕ РЕЗУЛЬТАТЫ КОМПЛЕКСНОГО ТРАДИЦИОННОГО ЛЕЧЕНИЯ БОЛЬНЫХ ПАНКРЕОНЕКРОЗОМ, ОСЛОЖНЕННОГО СЕПСИСОМ

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АБСТРАКТ

Актуальность. Анализ литературы за последние 10 лет показал, что сторонников консервативной терапии панкреонекроза с активной выжидательной тактикой становится все больше и больше. Для повышения эффективности лечебно-диагностической тактики сторонники такого подхода предлагают комплексы алгоритмов.

Материал. Проведен ретроспективное когортное исследование результатов комплексного обследования и лечения 97 больных с панкреонекрозом. Все больные находились на лечении и обследовании в Бухарском областном филиале Республиканского научно-практического медицинского центра экстренной медицинской помощи с 2013 по 2017 годы.

Заключение. Анализ результатов традиционных методов лечения панкреонекроза, осложненного сепсисом, показал наличие высокого уровня осложнений заболевания (38,1%) и летальности (30,9%), обусловленных отсутствием объективных критериев прогнозирования развития панкреатогенного сепсиса и синдрома полиорганной дисфункции, что требует проведение детальных исследований патогенетических механизмов этого грозного заболевания.

Ключевые слова: Панкреонекроз, синдром системной воспалительной реакции, сепсис как осложнение панкреонекроза, консервативное лечение, хирургическое лечение, непосредственные и отдаленные результаты