

# Retrospective analysis of clinical problems concerning acute pancreatitis in one treatment center

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## Abstract

**Introduction:** Severe acute pancreatitis is still a difficult clinical problem, it is a challenge for medical teams, which should include the strategy of personalized medicine. In clinical observations, among patients with the fulminating course of acute pancreatitis developed during the first hours leading to irreversible multiorgan failure and death.

**Aim:** To evaluate the frequency of occurrence and analyze the progression and treatment of severe acute pancreatitis (AP) in patients hospitalized during the years 2004–2010 at the Clinical Surgery Ward.

**Material and methods:** One thousand and fifty patients treated for AP were included in the study; 97 patients with severe AP were subjected to a detailed clinical analysis.

**Results:** The average age of the patients was 52.8 years. Relapses occurred in 14.9% of patients. The severe form of acute pancreatitis was diagnosed in 97 patients, which accounts for 9.2% of all the illnesses, and occurred significantly more often in male patients ( $p < 0.01$ ). The most frequent etiological factors were cholelithiasis (46.4%), and idiopathic pancreatitis (27.8%); alcohol consumption was responsible for 22.7% of the cases; the occurrence of both a bile-derivative and alcoholic factor was found in 3.1% of the cases. A worsening clinical state resulted in laparotomy in 26 patients (26.8%), and re-laparotomy in 5 patients. Necrosectomy was performed on 15 patients, of whom 33.3% died due to complications. The total mortality in severe AP was 38.1%. The average age of the deceased was 66.5. Early deaths within 14 days were noted in 78.4% of patients ( $n = 29$ ) who died due to severe AP.

**Conclusions:** Severe AP in spite of implementing modern diagnosis and treatment methods is still associated with a high risk of death. Constant clinical observation and use of available prognostic scales are essential in improving AP prognoses.

## Introduction

Acute pancreatitis (AP) is an acute inflammatory process of the gland itself, with progression to a greater or lesser degree of surrounding tissue or remote organs. The epidemiological data from the last few years indicate an increase in the frequency of occurrence of both acute and chronic pancreatitis. High geographical variation can be observed globally in the incidence of AP, ranging from 15.9/100,000 to 73.4/100,000 per year [1–4]. In Poland there are no studies of prospective epidemiological data concerning the incidence of pancreatitis. Data recently published for the Świętokrzyskie

Voivodeship indicate that in this region, AP affected 99.9/100,000 inhabitants. First-time incidents in the analyzed period of one year affected 79/100,000 inhabitants [5]. In the recently published retrospective study of the Trzebnicki district, the frequency of occurrence of AP in this area was estimated at 64.4/100,000 cases per year, of which 42.3/100,000 per year were first-time incidents [6]. Cholelithiasis and alcohol consumption, responsible for 80% of AP incidence, are the dominant etiological factors [7, 8]. It should be stressed that the so-called idiopathic or unexplained causes of AP are usually of microlithiasis etiology [9]. Endoscopic ret-

rograde cholangiopancreatography (ERCP), hyperlipidemia, drugs taken by the patient, hyperparathyroidism, sphincter of Oddi dysfunction, congenital defects, abdominal trauma, surgery, viruses, bacteria, parasites, autoimmune-based illnesses, and cystic fibrosis are among the less frequent causes [10]. In the majority of cases, AP has a benign course, characterized by a slight dysfunction of the organ, which regresses after conservative treatment. In about 20% of patients, the disease has a severe course and may lead to life-threatening multi-organ failure. Local and/or system-wide complications occur in the severe form of the disease. General complications may affect the cardiovascular system, the respiratory system, kidneys and disorders in hemostasis. Metabolic disorders, bleeding into the alimentary canal, and complications from the central nervous system may occur as well [11]. General mortality in AP is lower than 5%. In its severe form, hospitalization is prolonged as a result of pancreatic necrosis and multiple organ dysfunction, which leads to a much higher mortality rate [12].

## Aim

The aim of the undertaken research was to analyze the clinical course of AP and therapeutic indications for conservative therapy and surgical treatment in patients treated within the years 2004–2010 at the Clinical Ward of General, Oncological and Endocrine Surgery of the Voivodeship Hospital in Kielce. The results of the research in the selected aspects refer to a group of hospitalized patients suffering from the benign form of AP.

## Material and methods

### Subjects

One thousand and fifty patients treated for AP during the years 2004–2010 at the Clinical Ward of General, Oncological and Endocrine Surgery of the Voivodeship Hospital in Kielce were included in the research. Between 3500 and 3700 patients are treated at the ward every year. The inclusion criterion was clinical recognition of AP. All patients treated due to AP in the analyzed period were included in the research. The final diagnosis was based on medical history, clinical presentation, determination of  $\alpha$ -amylase activity in blood serum and urine and imaging examinations (ultrasonography (USG), computed tomography (CT), nuclear magnetic resonance (NMR), chest X-ray, or a plain film of the abdominal cavity). The criterion of qualifying for further analysis was the recognition of severe AP, and consequently the occurrence of one of the following factors: 1) local complications (necrosis, false cyst, pancreatic abscess); 2) multiple organ dysfunction

syndrome (MODS); 3) fulfillment of at least 3 criteria in the Ranson scale; 4) a result of 8 points or more in the APACHE II scale (Acute Physiology and Chronic Health Evaluation II). In the group of 97 patients with severe AP, the following data were included in the assessment: age, gender, cause and calculation of severity of AP by means of the Ranson and APACHE scale, previous treatment methods, complications, and mortality.

### Statistical analysis

In the study of significance of the mean difference, the parametric Student's *t*-test was used. The significance of difference between distributions was analyzed by means of the  $\chi^2$  test. In some cases the significance of difference between the indexes of structure was analyzed by means of "z" statistics. The null hypothesis stating that there was no significant difference was tested each time. The basis for possible rejection of the zero hypothesis, or stating that there was no reason for rejecting it, was a comparison between the value *p*, achieved in the test procedure, and a specified significance level of the test  $\alpha = 0.05$  (if  $p < \alpha$ , we reject the null hypothesis). The significance of difference in the women's ages was determined by means of the Z-test for the whole of the examined group ( $n = 1,050$ ). Interval estimation of the unknown age mean value for the whole population (the confidence coefficient  $1 - \alpha = 0.95$  was assumed). For some variables, instead of using the parametric Student's *t* test, one of the most effective nonparametric equivalents, the Mann-Whitney *U*-test, was used. The reason for selecting this test was that the consistency condition of a normal distribution (Gaussian distribution) for these quantitative variables (the consistency with normal distribution was analyzed by means of the Shapiro-Wilk test) was not fulfilled.

## Results

During the years 2004–2010, 1,050 cases of hospitalization for AP were registered at the Clinical Ward of General, Oncological and Endocrine Surgery of the Voivodeship Hospital in Kielce (final recognition K-85). There were 416 women and 634 men in the group. The average age of the patients was 52.8 years (the median was 51 years). The women hospitalized for AP were older than the men (the average was 61.1 years vs. 47.4 years; standard deviation was 17.8 and 15.8 respectively). During the 7-year period of the study, relapses of AP occurred in 14.9% of the patients (4.8% were female patients and 10.1% were male patients). Among this group, 57.7% of the patients were admitted to the hospital for a period of time shorter than 2 months before they became ill. A relapse was defined as another admission to the hospital without ascribing any time framework.

**Table I.** Characteristics of the group of examined patients with severe acute pancreatitis

Gender	Number	Average age	Maximum	Minimum	Median	Standard deviation	Value of <i>p</i>
Female	31	69.4	91	24	70	15.83	NS
Male	66	51.0	95	26	49.5	17.40	
Total	97	56.9	95	24	58	18.90	

NS – not statistically significant

**Table II.** Complications of severe acute pancreatitis

Complications of acute pancreatitis	Number of severe forms of acute pancreatitis	Percent of severe forms of acute pancreatitis
Aseptic necrosis	16	17
Infectious necrosis	28	28.9
Cysts and collection in the acute phase	22	22.7
Infectious liquid collection of the acute phase	35	36.1
Pleural effusion	42	43.3
Bleeding from the upper segment of the gastrointestinal tract	5	5.2
Limited intra-abdominal space	26	26.8

Some of the patients had more than one complication

Most patients with relapsing AP were readmitted to the hospital once (62.8%), 19.2% of patients were hospitalized two more times, several people were admitted to the Surgical Ward more than three times, and one person was treated fourteen times. According to the classification from Atlanta, the Ranson and APACHE scale, the severe form of AP was diagnosed in 97 patients, which accounted for 9.2% of total AP cases. The severe form of AP occurred significantly more often in male patients ( $p < 0.005$ ). The median age of the women was higher than that of the men (70 years vs. 49.5 years), but there was no statistical significance (Table I).

The most frequent etiological factor of severe AP was cholecystolithiasis, in 46.4% of patients (80.6% of females and 30.3% of males), alcohol was the cause of the illness in 22.7% of patients (28.8% of males and 9.7% of females), while both cholelithic and alcoholic factors were the cause in 3.1% of the patients (4.5% of males). An etiological factor was not recognized explicitly in 27.8% of cases (9.7% of females and 36.4% of males). In these cases, the most probable cause of severe AP was cholelithic etiology with the presence of micro-cholelithiasis. The average time of hospitalization for patients with severe AP was 25 days (minimum 1 day, maximum 128 days, median 19 days). In order to assess the degree of involvement of a disease and prognosis of complications and mortality the Ranson scale and APACHE II (the Acute Physiology and Chron-

ic Health Evaluation) scale were used; the assessment was performed during the first 24 h of the patient's stay at the ward. The average score in the Ranson scale was 2.1 (minimum – 0 points, maximum – 4 points, median – 2 points, standard deviation – 0.99), while in the group of patients who died it was 2.6 points. According to the APACHE scale the average score in the examined group was 11 points (minimum – 0 points, maximum – 34 points, standard deviation – 6.6 points). The average score in the APACHE II scale in the group of patients who died was higher than in the others (14 points vs. 11 points). During the first 24 h of hospitalization an ultrasound examination of the abdominal cavity was performed. Computed tomography (CT), which depended on clinical indication, was performed no earlier than 72 h after clinical symptoms appeared. The degree of morphological complications occurring in AP was determined by use of the computed tomography severity index (CTSI) drawn up by Balthazar *et al.* (Table II).

Vital signs were monitored in patients with severe AP, and positive fluid balance and analgesic treatment were applied. Carbapenems were used for protection against infection. In justified cases, targeted antibiotic therapy was used based on transdermal/transcutaneous biopsy or intrasurgical material. Antibiotics were used from 7 to 14 days. An intestinal and/or parenteral nutrition diet was begun after the assessment of the clinical state between the third and the fifth 24-hour

period of hospitalization. Within the analyzed cases, combined nutrition – parenteral and periodic intestinal feeding – was used in 80 patients, and only intestinal feeding was used in 17 patients. Early performance of endoscopic retrograde cholangiopancreatography (ERCP) (3 patients) was the method of treatment of acute biliary pancreatitis with symptoms of jaundice and cholangitis. After achieving improvement of the clinical state, usually after 4 to 8 weeks, a cholecystectomy was performed. Deterioration in clinical state was the reason for laparotomy in 26 patients (26.8%), and relaparotomy in 5 patients due to complications. The indication for laparotomy was infected necrosis with symptoms of sepsis (19 patients), diffuse peritonitis (5 patients), or bleeding into a pancreatic fluid cistern (2 patients). Necrosectomy with irrigation drainage was performed in 15 patients, including 5 patients (33.3%) who died after the procedure due to complications. One patient underwent cystogastrostomy in the late period of hospitalization. Laparotomy with different forms of closed drainage was performed in other patients. Among the registered complications after surgery in patients who underwent laparotomy, the most frequently observed complications were: infection of the wound (7 out of 26 patients; 26.9%), enterocutaneous fistula in 3 patients (11.5%), bleeding from the peritoneal cavity in 3 patients (11.5%), hernia in 2 cases (7.7%), and bleeding from the gastrointestinal tract in 4 patients (15.4%) (Table III).

In spite of implementing intensive treatment, 22 patients (22.7%) required transfer to the intensive care unit because of the following complications: acute respiratory distress syndrome (ARDS) in 27 persons, acute renal failure (25), circulatory insufficiency (34), hepatic failure (15), multiorgan failure (30), and sepsis

**Table III.** Complications after surgery

Complications after surgery	Number	Percent
Infection of the wound	7	26.9
Fistula	3	11.5
Bleeding from the peritoneal cavity	3	11.5
Eventration	2	7.7
Bleeding from the gastrointestinal tract	4	15.4

associated delirium (SAD – 14 patients). The total mortality in the group of patients who suffered from severe AP was 38.1% (37 patients). Among those who died the number who suffered from acute biliary pancreatitis dominated (21 people; 56.8%), but the etiology was not explained in 8 cases. The average age of the deceased was 66.5 years; the standard deviation was 18.7 (the average age of the others was 51 years; the standard deviation was 16.6). The influence of age on the frequency of deaths was determined to be ( $p < 0.0001$ ). The patients died most frequently during the first 3 days after their admission to hospital (20 people), while 9 more patients died within 14 days. Early deaths were defined as deaths occurring within 14 day after admission, and late deaths were defined as deaths occurring more than 14 day after admission. Early deaths, within the first 14 twenty-four-hour periods of hospitalization, were registered in total in 29 patients (78.4%), who died from severe AP. Among this group of deceased patients, 7 were treated with an open abdomen technique, and 5 people died within 3 days after being admitted to hospital (Table IV).

**Table IV.** Characteristics of early and late deaths in severe acute pancreatitis

Parameter	Early deaths (< 14 days), n = 29	Late deaths (> 14 days), n = 8	Value of p
Age	66.5 (26–91)	66.4 (46–87)	NS
Sex			
Female	11 (37.9%)	4 (50%)	NS
Male	18 (62.1%)	4 (50%)	
Etiology			
Alcoholic	7 (24.1%)	1 (12.5%)	NS
Biliary	15 (51.7%)	6 (75.0%)	
Idiopathic	7 (24.1%)	1 (12.5%)	
Ranson scale	2.4 (1–4)	3 (1–4)	
APACHE II scale	15 (5–34)	10 (4–20)	< 0.05
Infectious necrosis	6 (20.7%)	3 (37.5%)	NS
Aseptic necrosis	4 (13.8%)	3 (37.5%)	NS

NS – not statistically significant

For analyzing significant differences between the distribution of the variable "age" of the population of early and late deaths and for the mean values for the Ranson scale, the non-parametric Mann-Whitney *U*-test was used. The Student's *t*-test was used for analyzing the significance of differences for the average of the "APACHE II scale" parameter. The significance of differences between the distributions of the population of early deaths and the population of late deaths for both gender and etiology reasons was analyzed using a  $\chi^2$  test. The presence of infectious and aseptic necrosis was treated and tested as an index of the structure of the population of early and late deaths (*Z*-statistics were used). The *p* values showed that there was a reason for rejecting the null hypothesis (about equality of means, distributions, and indexes of structure) only when the APACHE II scale is taken into consideration. Here the null hypothesis was rejected at the significance level  $\alpha < 0.05$ .

## Discussion

Epidemiological data from different countries indicate that there is an increase in the number of patients suffering from AP. An analysis of hospitalizations between 2004 and 2010 indicated that the number of hospital admissions remained at the level of 150 yearly. The average age of the admitted patients was comparable with the tendency for higher incidence in older women than men, which was presented in the academic literature [10, 13, 14]. The confirmed frequency of relapses (14.9%) was lower than those reported in other studies [15]. Cholecystolithiasis was the most frequent etiological factor and alcohol the second. Endoscopic retrograde cholangiopancreatography may be the rarest cause of AP. In recently published research from our centre, AP after performing was recognized in 2.6% of the patients [16]. The general death rate due to AP, which was 3.7% in a group of 1,050 patients, was comparable with data from the academic literature [10, 14]. Age is depicted in the academic literature as a factor which increases mortality significantly [1, 14, 17, 18]. Such a tendency was also observed in our work but the statistical significance was not confirmed. Despite the development of medical science, a severe form of AP is still a big clinical problem with high risk of complications and a high death rate. Severe AP was recognized in 9.2% of the patients suffering from AP. Data from the academic literature indicate frequency of 15–20% of the severe forms of AP. The initial assessment of the severity of a disease has great prognostic importance. Markers of pancreatitis and/or markers of acute pancreatic necrosis are indicated among the isolated prognostic coefficients. The correlation of the

level of procalcitonin with the presence of infection with acute pancreatic necrosis and multi-organ failure is being sought [19]. Other research indicates the usefulness of analyzing the level of D-dimer, protein S and protein C between the first and third 24 h of a disease in prognostication of the course of AP [20–22]. However, because it is admitted that isolated prognostic factors are not effective in predicting complications, the recommended prognostic Ranson and APACHE II scales were used in the center of the authors of this work. Such an approach also has its limitations, because the results of the study show that severe course of disease was predicted using the Ranson scale for only one third of the patients. Using the APACHE II scale turned out to be more efficient in predicting disease severity. 54.6% of the patients who suffered from severe AP were given values  $\geq 8$ . The lack of possibility for taking into consideration the passing of time from the moment of the occurrence of symptoms until the time of hospitalization may have an influence on such a result, which was suggested in the studies conducted earlier [18].

The average score in the APACHE II scale in the group of patients who died was lower than in Gotzinger's research (14 points vs. 21 points) [23]. Using the APACHE II scale increased the opportunity of forecasting early deaths in a statistically significant way, which was also confirmed in other studies [24]. One needs to take into consideration that the APACHE II scale used during the day of admission to the hospital may become unreliable in diagnosing acute pancreatic necrosis [11, 25]. Treatment of the patients with severe AP was based on clinical indications, and included positive fluid balance and early enteral and parenteral nutrition. The most recent studies show a positive effect of administering fluid therapy with the use of mainly crystalloids in the first hours of hospitalization [26]. Early enteral nutrition can have an influence on the limitation of hypermetabolism due to the developing systemic inflammatory reaction and can limit the occurrence of organ failure as well as cutting down the time of hospitalization [27].

The indications for surgery in AP have changed in recent years. In 2002 the International Association of Pancreatology worked out guidelines concerning surgical treatment of AP, from which it results that infectious necrosis with symptoms of sepsis is a valid reason for surgical intervention and radiological drainage. A surgical procedure needs to be taken into consideration no earlier than 14 days after the beginning of the disease unless there are reasons for earlier intervention [28]. Emphasis is placed on maintenance treatment and prevention of infection of necrosis and other complications. Minimally invasive surgical and endoscopic necrosectomy is performed in necessary cases [29].

In studies comparing the effects of early and late surgical intervention, it was shown that mortality rate was lowered among patients for whom late exploration of the abdominal cavity was performed. Generally, the mortality rate among patients with severe AP decreased from 39% to 12% [30]. In another study it was shown that the mortality rate was lowered among the patients for whom the operation was performed 29 days after the beginning of the disease in comparison with those patients who underwent the operation between the 1<sup>st</sup> and 14<sup>th</sup> days (8% vs. 75%) [31]. In the analyzed material, the postoperative mortality rate was high at 33.3% in comparison with the academic literature: 16.3% [18], 18% [32], and 36% [31]. In our material, 5 patients who were operated on died during the first 3 days of their stay in hospital.

The dynamics of the course of the severe form is sometimes diversified. Systemic inflammatory response syndrome (SIRS) with accompanying multiorgan failure becomes a cause of early death in the first 24 h of hospitalization. Even intensive shock-controlling treatment, kidney replacement therapy, and respiratory therapy in respiratory failure may be largely ineffective for some of the cases of the severe form. The mortality rate in the severe form may reach 20%, increasing to 25% in infectious necrosis and to 50% in organ failure [10, 33, 34]. In the studies of five European countries, the overall mortality was 7.8%, but in the necrotic form was 16.1% [34]. In the analyzed material the mortality rate in the severe form of AP was higher than that presented in the academic literature and reached 38.1%. Such a high death rate was caused by early deaths resulting from an incredibly quick and dramatic course of severe AP. The high percentage of registered deaths caused by severe AP was partly connected with more frequent hospital admission of patients in poor general condition who were handed over from other hospitals of the Voivodeship to a clinical ward. The consumption of very large amounts of alcohol by patients who died also had a significant influence on mortality. A higher death rate was registered for the lithiasic etiology of severe AP: 56.8% of all the causes. A connection between etiology and gender, and frequency of the occurrence of early and late deaths was not found. In research from Taiwan, more frequent occurrence of early deaths from an alcoholic etiology and late deaths from lithiasic etiology were reported [18].

In clinical observations, among patients with the fulminating course of AP, severe toxemia developed during the first hours, leading to irreversible multiorgan failure and death. Early development of renal failure, shock and hepatic failure were observed as causes of early death with fulminating AP [24]. Taking the most

aggressive methods of treatment against acute respiratory distress syndrome (ARDS), ventilation, acute renal failure (hemodialysis), applying pressor amines (noradrenaline, dopamine), antibiotic therapy, and fluid therapy may be ineffective and lead to the patient's death. The severe forms of AP of a diverse course often present as acute pancreatic necrosis of varying severity and affect peripancreatic tissues and retroperitoneal phlegmon. Such a state of the disease creates a temporary opportunity to consider different methods of treatment: cholangiopancreatography, sphincterotomy, drainage, necrotomy, irrigation drainage, and possible repetition of laparotomy. The continuation of intensive preventive treatment, struggle with sepsis, acute renal failure, thrombotic and embolic as well as circulatory complications, connected with intervention methods, may provide a chance to save the patient's life.

## Conclusions

Despite implementing modern methods of diagnosis and treatment, the severe form of AP still involves a high risk of death. In clinical practice we meet patients with a fulminating course of AP, which leads to irreversible organ failure, and the death of a patient during the first days. In prognosis of the course of AP, constant clinical observation is valid and it is also important to make use of the accessible prognostic scales, from which the APACHE II scale turned out to be the most useful. Its use significantly increased the possibility of predicting early deaths. Early surgical treatment is connected with a high risk of complications and mortality.

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