



**University of Medicine and Pharmacy of Craiova**

**DOCTORALE THESIS**

**Algorithm for diagnosis and treatment of biliary etiology of  
acute pancreatitis**

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**biliary acute pancreatitis, cholecystectomy, amylase, severity index, necrosectomy , pseudocyst**

**1.Introduction**

After 100 years from the first pathogenic hypothesis issued by OPIE (1901), acute pancreatitis remain a disease over which still hangs controversies and uncertainties caused by a serious and unpredictable evolution.

Modern acquisitions of intensive care, diagnostic and minimally treatment, linked with the experience accumulated over several decades of observation of disease were the main reason for the changes adopted by a lot of conferences (Marsilia 1963 and 1984, Cambridge 1983, Atlanta conference 1992). Thus were developed international guides of diagnosis and treatment(UK Guidelines1998 and IAP Guidelines 2002) which defined the mains forms of anatomic and clinical disease and decided the diagnostic and therapeutic algorithm.

Acute biliary pancreatitis, considered to be a complication of biliary lithiasis is the main etiological form of acute pancreatitis and the only form of acute pancreatitis that receiving pathogen treatment.

The risk of developing an acute biliary pancreatitis is higher in men with gallstones, but due to a higher incidence of gallstones in women overall incidence of acute biliary pancreatitis is higher in women.

The main conceptual change in this case is in the early phase a therapeutic and conservative therapy , ( the first 10-12 days of the disease) and surgery in the the second phase.

Over several decades of activity, the Department of Surgery Craiova has like priority the study of acute pancreatitis and a valuable experience in a series of papers published in national and international journals.

This was the main reason where I decide to redeem the experience of the Department of Surgery Craiova in a scientific research that represent an objective assessment about diagnosis and treatment of acute biliary pancreatitis.

## **2. Acute pancreatitis**

### **2.1 Etiopathogenesis**

The incidence of acute pancreatitis is different within wide limits ,depending on etiology, age, gender, dietary habits, (there was no seasonal determinism) being assessed an average of 5-80 / 100,000 inhabitants. In Romania the incidence is 20 / 100,000 inhabitants (1).

#### **2.1.1 Etiology**

Acute pancreatitis is a disease with a plurifactorial etiology that have incriminated a lot of etiopathogenic circumstances including biliary disorders and alcohol which are the most common of all.

Biliary disorders are the most common cause of acute pancreatitis, gallstone is responsible for 30-60% of acute pancreatitis cause-effect association and a valid cancellation risk of recurrent disease after cholecystectomy elimination of extrahepatic biliary lithiasis (2.3). This risk decreases after Endoscopic sphincterotomy and also after a treatment with ursodeoxycholic acid [3].

#### **2.1.2. Pathogenesis**

P.A Pathogenesis is incomplete and controversial. Till now were issued five pathogenic theories (canalar Opie, vascular, infectious, allergic, nervous). But none of them in isolation does not provide a satisfactory explanation of all pathogenic mechanisms and pathophysiological changes of acute pancreatitis. Currently, two theories have been proposed to interpret premature intracellular proteolysis..trypsinogen activation theory and location theory which trypsinogen is transformed into active trypsin by lysosomal hydrolases. The pathogenesis of acute biliary pancreatitis is related to the migration of a biliary stone through duodenal

papilla, the mechanisms that induce the disease are: the duodenal juice reflux into the pancreatic duct due to transient dysfunction of Oddi sphincter, secondary to a stone migration and / or secondary to an increased pressure in the pancreatic duct after its sudden obstruction, which leads to an activation of proteolytic pancreatic enzymes [5], with the addition of bile infection.

## **2.2. Morfopatologie**

Current data suggest that the severity of P.A and her pathologic support are defined in the early hours. The pathological classification of pancreatitis is divided into 2 main categories:

- acute pancreatitis with necrosis, the substrate mild (edematous PA)
- hemorrhagic -necrotic acute pancreatitis , severe forms substrate; [2, 6

The two forms have the same pathogenic mechanism, but not the evolutionary stages of the same disease, which are completely different [91].

## **2.3. Diagnosis of acute pancreatitis**

Diagnoses of acute biliary pancreatitis include 3 stages: positive diagnosis of acute pancreatitis, the etiology and the severity.

## **3. Treatment**

Therapeutic attitude is different depending on the severity of the pancreatitis and its response to conservative medical treatment.

## **4. Material and method**

In light of the literature and experience of Surgical Clinic of Craiova, I did a comprehensive study of acute biliary pancreatitis, following the objectives:

- identify etiopathogenic risk factors
- the clinical study and difficulties diagnostic of acute biliary pancreatitis

- establishing objective, criteria of gravity, allowing the classification of biliary acute pancreatitis in its correct category
- the assessment of biological syndrome as a factor in assessing the severity of acute biliary pancreatitis
- to evaluate the contribution of the main positive diagnosis an investigations, the assessment of severity, tracking the dynamic evolution to early diagnosis of developmental complications, especially those threatening.
- establishment of well standardized indications that moment, technique, duration, etc. for each of the two fundamental therapeutic means: conservative therapy and surgery
- establish a close monitoring of dynamic evolution during hospitalization and after discharge the patient
- improve prognosis and reduce morbidity ,mortality and postoperative

To achieve the above mentioned objectives we performed a retrospective and prospective on a number of 123 cases of acute biliary pancreatitis, selected from (400 ) hospitalized and treated acute pancreatitis in Surgical Clinic of Craiova in 10 years (2002-2011) .

Etiology of acute biliary pancreatitis was established by the conjunction of:

- clinical criteria ,female. aged 50 years , suffering of biliary lithiasis with or without previous confirmation
- biological data (increased levels of bilirubin with predominance of the conjugated fraction , increasedalkaline phosphatase,values - three times higher than normal, liver enzymes, especially GOT/ASAT , and imaging examinations : simple abdominal ultrasound.

## **5. Demographics data**

Acute biliary pancreatitis, as a complication of the biliary lithiasis, is a well distinct entity among the acute pancreatitis, credited with a weight up to 60% of all

etiological forms of acute pancreatitis [1, 2, 3]; equaled or exceeded in the last decades by the alcoholic pancreatitis (36.75% vs 30.75% alcohol vs biliary acute pancreatitis in our study), the two etiological forms representing almost 75% of the total cases of acute pancreatitis [4]. Its incidence ranged widely: 4.8-24/100,000 inhabitants in Western Europe, 17/100,000 inhabitants (220,000 new cases/year) in the USA and 5-80/100,000 inhabitants in Japan [1]. The risk of developing an acute biliary pancreatitis is higher in men with gallstones, but due to higher frequency of gallstones in women overall incidence of acute biliary pancreatitis is higher in women (sex ratio F/B = 1.15 in our study).

I have not noticed significant differences in the distribution of acute pancreatitis according to area and origin, in terms of the incidence of acute biliary pancreatitis patients from rural areas because it was evident: 87 vs 46 for the rural people area without finding an explanation that would satisfy us in this finding.

## **6. The diagnosis of acute biliary pancreatitis**

- includes 3 stages: positive diagnosis of acute pancreatitis, the etiology and the severity.

### **6.1. Positive diagnosis of acute pancreatitis**

was based on clinical and biological criteria stated at the Consensus Conference in Atlanta in 1992, reaffirmed in 2001 by the National Consensus Conference of the French Society of Gastroenterology and updated in 2012 [6]: sudden onset of abdominal pain with dorsal irradiation (113 = 91.86% cases) and increased level of serum amylase more than 3 times the normal (111 cases = 90.24%). When these elements were not conclusive enough we appealed to computed tomography with contrast IV (62 cases = 50.01%) and endoscopic ultrasound (46 cases = 37.39%).

### **6.2 Etiologic diagnosis of acute biliary pancreatitis**

**Biliary etiology** was suggested by clinical signs (female, over 50 years, with a history of biliary pain) and biological syndrome (ALT 3 times higher than normal, increasing alkaline phosphatase and total bilirubin, although that increased direct

bilirubin is rather a biliary obstruction sign, than of the biliary etiology) and confirmed by imaging investigations whose value is uneven. Ultrasound is credited with a sensitivity of 87-98% for the detecting gallstones (67% in the initial stage due to ileus) and only 30% for bile duct stones, while EUS has a sensitivity of 100% and sensitivity of 91 % for common bile duct stones, while cholangio-MRI has a sensitivity of 81-100% for detecting common bile duct stones, with a negative predictive value of 98% and 94% positive predictive value. Computed tomography and magnetic resonance imaging conversely are credited with a sensitivity of 78% and specificity of 86%, respective 83% and 94% for the diagnosis of severe acute pancreatitis [1].

### **6.3 Diagnosis of gravity**

Diagnosis of gravity, based on the known criteria (bio-clinical scores, computed tomography and organ failure) revealed a greater number of severe acute pancreatitis (50.4%), although the literature mentions the incidence of severe biliary pancreatitis up to 35% [1, 8].

## **7. Diagnosis and local complications of acute biliary pancreatitis**

Severe acute biliary pancreatitis may develop general and local complications, including infection of necrosis and pancreatic pseudocyst that are the most common and powerful local complications that can decisively influence the evolution and prognosis.

### **7.1. Pancreatitis infection**

Pancreatic infection, defined as the presence of microorganisms (bacteria or fungi) in the multiplication of the pancreas and peripancreatic tissue was found in 17 (27.41%) severe biliary acute pancreatitis: 15 cases infected necrosis, pseudocyst pancreatic abscess infected 1 case .

Bacteriological examination of pus collected by needle aspiration or intraoperative was performed in all cases and we found in 58.62% (10) of the cases that the infection was monomicrobial in 52.28% (9) of the cases the infection given by gram-negative. The germs involved in the order of frequency were Esherichia coli, enterococci, Staphylococcus aureus, Klebsiella, Pseudomonas and Proteus.

## **7.2. Pancreatic pseudocyst**

Pancreatic pseudocyst is the main complication (3-6 weeks) of severe acute pancreatitis, the incidence of complications (10-15% in the literature) is increasing with severity of pancreatitis.

Pancreatic pseudocyst was encountered in 14 cases of acute biliary pancreatitis, representing 30.43% of all pancreatic pseudocysts encountered in the study period analyzed. Comparing the incidence of pseudocysts in general to that of acute biliary pancreatitis pseudocysts we have found that it is significantly lower (16.19% vs 11.38% overall PA PAB) and in terms of the ratio the severe acute pancreatitis including all forms of etiological cause. Complication was seen in all ages, with maximum incidence in the age groups 51-60 and 61-70 years, and in women (5 men / 9 women - sex ratio = 1 / 1.8).

Although literature mentions that pancreatic pseudocyst may also occur in the development of mild and / or moderate acute pancreatitis in personal study, all pseudocysts occurred in the evolution of severe acute biliary pancreatitis (5 cases with jaundice and without jaundice angiocholitis and angiocholitis 9 cases).

## **8 . The treatment of acute biliary pancreatitis**

Instituted immediately after the diagnosis was a complex surgery with an adaptive algorithm of the clinical and therapeutic response.

### **8.1 Aggressive conservative medical treatment**

It was applied in all cases, and was the treatment of choice, carried out under continuous monitoring of vital signs and repeated reassessment and consisted of: --- aggressive volume replacement; upper digestive aspiration and progressive resumption of oral nutrition on digestive tolerance measure recurrence; If parenteral nutrition gastrointestinal intolerance persists after 4-7 days, depending on the saturation of oxygen O<sub>2</sub>, antacids (H<sub>2</sub> receptor antagonists, inhibitors of the pump H<sup>+</sup>), pancreatic antisecretory - octreotide, analgesics, antibiotics to patients with angiocholitis (bile sepsis), or prophylactic in If the pancreatic necrosis or collections are documented

peripancreatic CT edical and / or surgical, as an adaptive algorithm of the clinical and therapeutic response.

## **8.2 . Surgery treatment**

In acute biliary pancreatitis with jaundice and angiocholitis, cholecystectomy and bile duct decompression is the treatment of choice [4], open cholecystectomy with intraoperative cholangiography being the standard recommendation in the 80s [9]. Introduction of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy as the methods of diagnosis and treatment of common bile duct stones in severe acute biliary pancreatitis, gave rise to many controversies regarding its indications and moment of use for these patients [10, 11, 12]. The difficulties towards decision of using early ERCP for the treatment of severe acute biliary pancreatitis depends on [13]: the difficulties of the diagnosis of a concomitant cholangitis, the lack of an effective ways to predict the outcome and on the fact that the predictive value of each evaluation system not exceed 50-60%, which lead to errors in classifying the acute pancreatitis in mild or severe. More than that, the biliary stones were found only in 50% of cases in which the emergency ERCP was performed, exposing the patients to the known risks of ERCP (acute pancreatitis post-ERCP, bleeding, and perforation of the duodenum), encumbered with a mortality of up to 13% without any benefit [14]. UK Guidelines recommended emergency therapeutic ERCP for all the patients with acute pancreatitis, with suspected biliary etiology and prediction of severe acute pancreatitis or cholangitis, jaundice or concomitant expansion of common bile duct [15], while the AGA Guidelines [13] are more restrictive, proposing making early ERCP only in patients with cholangitis or suspected common bile duct stones (dilated common bile duct with visible calculus, jaundice and abnormal liver tests). Persistent biliary obstruction over 48 hours is considered the best indicators for emergency ERCP [16]

## **8.3. Local PAB treatment of complications.**

### **8.3.1 Treatment of infected necrosis**

Surgery was practiced in all 16 infected necrosis and following the objectives:

removal of all infected tissue; prevention of late complications such as pancreatic abscess, with high mortality, by removing infected pancreatic infection, the lavage areas and peripancreatic that providing adequate drainage after debridement and preserving the maximum viable pancreatic tissue. . The moment of Necrosectomy was after at least 12-14 days while the disease was installed , when the necrotic areas mature well individualized and separated by healthy pancreatic tissue can be easily removed by digitoclasie.

Necrosectomy was carried out like:

□ as a primary operation, together with conventional cholecystectomy in 8 pancreatitis with jaundice and angiocholitis, the infected necrosis was installed during the conservatively medical treatment .

□ as reoperation in 8 jaundice and cholangitis patients that were imposed early cholecystectomy and decompression (5 days) of bile duct and necrosis infection occurred during the postoperative evolution

The behavior of the cavity after necrosectomy was the multiple external drainage in 8 cases, 4 semilaparostomie cases and irrigation / aspiration in 4 cases.

The pancreatic abscess encountered in the evolution of patients with biliary acute pancreatitis was resolved by CT guided drainage.

### **8.3.2 Pancreatic pseudocyst treatment**

The current therapeutic approach in pancreatic pseudocyst developed significant changes beginning with major diagnostic and therapeutic strategy of acute pancreatitis, pancreatic pseudocyst has two treatment options: conservative therapy, coupled with monitoring and dynamic tracking to complete resorption and pseudocyst drainage (surgical or percutaneous CT guided ultrasound and endoscopic), each of this with good pseudocyst indications depending on the type, location, size, evolution, presence or absence of complications and not least the patient's general conditions and treatments available. In all the 14 pancreatic pseudocysts cases of acute biliary pancreatitis was used the therapeutic procedures like :

□ the conservative therapy (9 cases) in uncomplicated pseudocysts with D <6 cm, in at least 4 weeks after the onset of severe PAB without clinical expression after solving this acute pancreatitis with good digestive tolerance. The patients followed this dynamics (clinical, biological and imaging) for at least 6 months to complete the resorption or decreasing the diameter .

the drainage was required in 5 pseudocysts with D> 6 cm that occurred in 4-6 weeks after the onset of acute biliary pancreatitis , symptomatic (persistent epigastric pain, gastrointestinal intolerance, early satiety) and / or complicated. Were used the following processes:

direct endoscopic transmural drainage (transgastric)- 2 cases

-an open surgery - 2 cases

-a CT guided drainage one with 1 infected PP

## 9. Results

The evolution of patients was followed by clinical, biological and imaging attention during the hospitalization and regular checks (outpatient or inpatient) at 1, 3 and 6 months. Proceeding in this manner, the 156 severe acute pancreatitis revealed the following possibilities:

□ 107 (86.99%) - favorable evolution remission of clinical phenomena, biological and imaging changes

□ 12 (19.35) severe acute pancreatitis - unresponsive to conservative treatment

□ 16 (13.0%) - local evolutionary complications in 16 cases (13%)

□ 16 (13.0%) deaths

The postoperative morbidity (Table No. 15) was 18.8% (16 cases), in eight local complications (1 pancreatic fistula, intestinal obstruction 1 and / eventrations 6) and

eight general complications (cardiovascular 2, thromboembolism 1 upper gastrointestinal bleeding 1 hepato-renal insufficiency MODS 1 and 3) the rate of conversion was 9.83% (6 cases): 6.38% by laparoscopic cholecystectomy performed for acute biliary pancreatitis respectively in the severe 16.6%, the conversion being imposed by the difficulty of identifying anatomical elements . Recorded to 16 deaths, with an overall mortality rate of 13% and a postoperative mortality of 9.75%, 1.6% and 17.74% and severe mild pancreatitis.

-detailed analysis predominance of death among male patients (ratio B / F = 11/6) and in age groups over 60 years in accordance with the general distribution by age and sex in case of an severe acute pancreatitis

-severe forms of acute pancreatitis who developed adverse and provided deaths were encumbered in almost all cases a pathologic pre-existing cardiovascular disease 7 cases, 4 cases of grade III obesity, diabetes 2 cases, 2 cases of liver cirrhosis, chronic respiratory failure 1 case.

-criteria for classification in the severe form of acute pancreatitis have been met in all cases that evolved the death: Ranson score > 3 admission, presence and / or worsening of organ system dysfunction (MSOF 10 IRA 2 3 ARDS, renal liver 1) and TC confirmation of pancreatic necrosis with ISTC > 6 in 8 cases

-4 cases by shape ending with death within 48 hours of onset; All this cases finally confirmed the autopsy

□-early surgery (11 cases) provided 7 of deaths. The operation of choice in early cases was made in duodeno-pancreatic drainage ± takeoff, the indication for surgery was still unresponsive to that conservative treatment. In 5 cases, surgery was delayed and imposed by the unfavorable development, with foci of necrosis infection (4 cases infected necrosis and pancreatic abscess 1), confirmed by clinical, biological and imaging, the surgery used the necrosectomy with closed drainage (2 cases) or semi laparotomie (3 cases).

## 10. Conclusions

1. Acute biliary pancreatitis is the main etiological form of acute pancreatitis, despite the fact that it was surpassed by acute pancreatitis in personal study of ethanol (30.75% vs. 37.75%).
2. The risk of developing an acute biliary pancreatitis is higher in men with gallstones, but due to a higher incidence of gallstones in women overall incidence of acute biliary pancreatitis is higher in women, as confirmed by personal study that found the incidence of biliary acute pancreatitis cause higher in men (68 men vs 55 women, sex ratio = 1.23 / 1).
3. The age ranged between 31 and 84 years, with peak incidence in the age group 50-60 years and female sex predominance .
4. The diagnosis of acute biliary pancreatitis includes 3 stages: positive diagnosis of acute pancreatitis, the etiological diagnosis and diagnosis of gravity.
5. The pathogenesis of acute biliary pancreatitis is related to the migration of a biliary stone through duodenal papilla, the mechanisms that induce the disease are: the duodenal juice reflux into the pancreatic duct, secondary to a stone migration and / or secondary to an increased pressure in the pancreatic duct after its sudden obstruction, which leads to an activation of proteolytic pancreatic enzymes [5], with the addition of bile infection [1].
6. Positive diagnosis of acute pancreatitis has been established on the basis of clinical and biological data stated by Consensus Conference in Atlanta in 1992, updated in 2011: sudden onset of abdominal pain with dorsal irradiation and increased serum amylase more than 3 times the normal value . When these elements were not conclusive enough we appealed to computed tomography with contrast iv or endoscopic ultrasound .
7. Etiology of acute biliary pancreatitis was established by the conjunction of clinical criteria, female aged 50 years, suffering of biliary lithiasis with or without previous confirmation, the presence of jaundice and / or clinical signs of angiocholitic ,biological

data (increased levels of bilirubin with predominance of the conjugated fraction , increased alkaline phosphatase, values - three times higher than normal, liver enzymes, especially GOT/ASAT , and imaging examinations : simple abdominal ultrasound.

8. . Increased incidence of severe acute biliary pancreatitis (51.21%), evaluated against the criteria known (scores bio-clinical, CT, presence shortcomings of organs and systems) compared with the literature that recognizes an incidence of severe forms of pancreatitis gall to maximum 35%;

9. significantly increased incidence of infection of necrosis in acute biliary pancreatitis in front of other etiological forms (27.4% vs 12.82%) and lowest for pancreatic pseudocyst (11.38% vs. 16.19%)

10. In acute biliary pancreatitis with jaundice and severe angiocholitis (19 cases), surgery was performed within 5 days of onset (median 3) and had as the main objective the bile duct decompression, achieved by open cholecystectomy + choledocolithotomy+ Kehr drainage (11 cases) or choledocoduodenostomy (1 case). In 4 cases with normal common bile or unapproachable due to the inflammatory process, the operation was limited to cholecystectomy and drainage of pancreatic lodge.

11. Early ERCP may be the method of choice in patients with suspected cholangitis or persistent common bile duct stones (dilated common bile duct with visible stone, jaundice and abnormal liver tests).

12. In acute biliary pancreatitis without jaundice and severe angiocholitis, we preferred to perform surgery after 10 to 14 days from the onset, during which patients were monitored using clinical, biological and imaging tests (ultrasound, EUS, CT). In patients with favorable outcome after medical treatment and with no gallstone in common bile duct or its expansion revealed by imaging tests, laparoscopic cholecystectomy was elective; in cases with unfavorable outcome and lack of response to conservative therapy with infected necrosis signs, the operation consisted of open cholecystectomy.

13. Pancreatic pseudocyst (14 cases = 30.42%), the main complication of severe acute pancreatitis , has two treatment options: conservative therapy for uncomplicated pseudocysts, and drainage reserved pseudocysts with D > 6 cm symptomatic and / or

complicated, which can be achieved endoscopic transmural or transpapillary, surgical or percutaneous guided imaging.

14.Results: the conversion rate of 9.83% (6.38% in laparoscopic cholecystectomies performed for mild acute biliary pancreatitis or 16.6% in the severe forms), 18.8% postoperative morbidity and mortality rate (13% overall mortality, postoperative mortality 9.75%, 1.6 % for mild pancreatitis and 17.74% for severe ones) fits within the literature data.

