

# Severe acute pancreatitis

## Clinical forms of different gravity



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### Severe pancreatitis. Clinical forms of differential gravity

**INTRODUCTION AND AIMS:** Severe Acute Pancreatitis (SAP) is characterized by some degree of severity. The aim of this study is to identify within severe forms the critical, early severe acute pancreatitis (ESAP).

**METHODS AND PATIENTS:** Since 1997 to 2011 we have treated 276 acute biliary pancreatitis. SAP was 21.7% (60); among SAP were defined 13 (21.6%) ESAP as presence of organ dysfunction within 72 hours after onset of symptoms. Clinical features, organ failure, therapeutic choices and results between SAP (47) and ESAP (13) were compared.

**RESULTS:** The comparison has shown the following results: impairment degree of pancreas (Balthazar CT score): SAP 2.3 – ESAP 3.85; abdominal compartment syndrome (ACS): ESAP 7.6% (1/13); MODS: ESAP 46.1% (6/13); single organ dysfunction: SAP 51% (24/47) – ESAP 53.8% (7/13); hypoxemia: SAP 65.9% (31/47) – ESAP 76.9% (10/13); pancreatic infections: SAP 6.3% (3/47) – ESAP 23% (3/13); mortality: SAP 4.2% (2/47) – ESAP 15.4% (2/13).

**DISCUSSION:** ESAP is characterized early by major incidence of ACS, MODS, impairment degree of the pancreas. In a later phase the gravity of severe pancreatitis lies on the septic complications of fluid necrotic collections. In ESAP the mortality is higher: 15.4% because of multiorgan dysfunction (in first phase); in SAP is 4.3% because of septic complications (in later phase).

**CONCLUSIONS:** Treatment of SAP and ESAP is now more conservative and less invasive than in the past: intensive care, prevention of intestinal failure and assure papillary patency in the first phase of the disease. In the later phase therapeutic procedure for fluid necrotic collections is US/CT percutaneous catheter drainage.

**KEY WORDS:** Early severe acute pancreatitis, MODS, SIRS

### Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas with prevalence of biliary pathogenesis characterized by different degrees of severity: from a mild ede-

matous-interstitial inflammation, which is a self-limiting disease, to a severe type with local necrotizing inflammation and systemic complications<sup>1</sup>. In the last years the nosography of AP has undergone various evolutions and modifications. According to the Atlanta classification and its various modifications, severe acute pancreatitis (SAP) is defined as associated with local and/or systemic complications<sup>2,3</sup>. Development of persistent organs failure within 72 hours of symptoms onset and/or of infected pancreatic complications allows the definition of the most severe forms, identified as critical, early severe acute pancreatitis (ESAP). Critical forms (ESAP) are characterized by a short course, progressive multiple organ dysfunction syndrome (MODS), early hypoxemia, high CT severity index, increased incidence of necrosis,

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infection and abdominal compartment syndrome. ESAP mortality rate can be very high: 40% according to literature <sup>1,2-6</sup>. Aim of this study is to identify within severe forms, early critical severe acute pancreatitis and to illustrate their clinical appearance and their therapeutic choices.

## Materials and Methods

In the period September 1997/December 2011, 924 patients with biliary lithiasis were hospitalized in our department of General Surgery: 555 gallbladder lithiasis, 276 acute biliary pancreatitis (ABP) and 93 choledocholithiasis without pancreatitis. The demographic data of the patients with ABP were: mean age 49 years (range 40-86 years) and female to male ratio 1.33:1. Biliary pathogenesis was confirmed in all patients: cholecystic lithiasis or biliary sludge was present in 100% of cases, while common bile duct size was >8mm in 40.7% of cases. The majority of our patients presented a clinical picture of mild/moderate forms. Mild pancreatitis are self limiting forms characterized by edema and normal enhancement of pancreatic parenchyma on contrast-enhanced CT. In moderate pancreatitis there are early acute fluid collections located in or near the pancreas and minimal and transient organ dysfunction without wall of fibrous tissue, almost always with spontaneous regression. Mild/moderate pancreatitis were 216/276 (78.2%), out of which 33/216 (15.2%) were moderate/severe. Moderate/severe forms are characterized by great peri-pancreatic and pancreatic involvement with fluid/necrotic collections but organ failure is transient or absent. Severe forms are characterized by diffuse or local areas of non viable pancreatic parenchyma, peri-pancreatic fat necrosis, non enhanced pancreatic parenchyma and/or fluid-necrotic peri-pancreatic collections with persistent or transient organ failure. Within the severe forms there are also critical or early severe forms with persistent or transient organ failure and infected pancreatic and peri-pancreatic collections. SAP were 60/276 (21.7%), out of which 13/60 (21.6%) were ESAP. We

have applied CT severity index with Balthazar scoring for the grading of acute pancreatitis and points for necrosis. This classification is based on morphological and functional features: focal or diffuse enlargement of the pancreas, pancreatic gland abnormalities, peri-pancreatic inflammation with pancreatic and peripancreatic fluid collection, areas of non enhanced parenchyma (Table I). In both groups of patients, severe (SAP) and critical forms (ESAP), the therapeutic approach is the same and is based on intensive care, fluid resuscitation, correction of hypoxemia and enteral nutrition; the evolution is followed controlling and treating the infection of necrotic tissue and peri-pancreatic fluid collections. In case of biliary pancreatitis, the therapeutic program includes assuring papillary patency and common bile duct cleaning <sup>7-17</sup> with endoscopic retrograde cholangiopancreatography/endoscopic sphincterotomy (ERCP/ES) <sup>18,19</sup>. After ERCP, it is necessary to perform laparoscopic cholecystectomy to complete gallstones treatment. The timing of laparoscopic cholecystectomy is connected with acute pancreatitis evolution because it is preferable to wait for the stabilization of the general conditions. Treatment of the later phase of acute pancreatitis consists in control and treatment of local complications: infections, haemorrhage, pancreatic and peri-pancreatic fluid necrotic collections. In our study we identify among severe acute pancreatitis the critical forms with particular early severity. The data of these two groups of patients are compared by means of statistical analysis with chi-square test and t-student test, with c.i. 0.95.

## Results

The comparison between the patients with SAP (47) and ESAP (13) has shown the following data: the degree of pancreas impairment with Balthazar score was 2.3 in SAP vs 3.85 in ESAP, abdominal compartment syndrome (ACS) was demonstrated in only 1 patient with ESAP (7.6%), MODS in 6 patients with ESAP (46.1%), simple organ dysfunction in 24 patients with SAP (51%) vs 7 patients with ESAP (53.8%), pancreatic sepsis in 3 patients with SAP (6.3%) vs 3 patient with ESAP (23%), hypoxemia in 31 patients with SAP (65.9%) vs 10 patients with ESAP (76.9%). Mortality rate was 4.24% in SAP vs 15.4% in ESAP. The result of the comparison of critical, early severe forms and severe pancreatitis is showed in Table II. The difference between SAP and ESAP has statistical significance for: degree of pancreas impairment (Balthazar CT score), abdominal compartment syndrome, treated in emergency with open approach, MODS and mortality (Table III). In summary, in our experience, we have classified within severe acute pancreatitis, some patients with most severe forms, particularly at the onset of the disease, with high degree of pancreas impairment and great involvement of general conditions: ACS, multiorgan dysfunction, etc.

TABLE I - Demographic data percentage incidence of biliary lithiasis and cholestasis indexes. CT severity index: CT Grade Point + point for necrosis (Balthazar). 276 acute biliary pancreatitis

Mean age	Sex	DIR. BIL < 2 mg	DIR. BIL 2-5 mg	AST/ALT x 3	G-GT >200	CBD size (US) > 8mm	Colecystic Lithiasis
49 (40-86)	F 158 M 118	60.4%	39.6%	26.8%	59.9%	40.7%	100%

  

Grade B1	183 (66.3%)
Grade C2	93 (33.6%)
Grade D3	47 (17.02%)
Grade E4	13 (4.7%)

TABLE II - Comparison of the clinical appearance of ESAP and SAP

	SAP (47)	ESAP (13)
Impairment degree of pancreas (Balthasar CT score)	2.3	3.85
Abdominal compartment syndrome ACS (%)	-	7.6% (1/13)
Multiple organ dysfunction syndrome	-	46.1% (6/13)
Single organ dysfunction	51.1% (24/47)	53.8% (7/13)
Pancreatic sepsis	6.3% (3/47)	23.1% (3/13)
Hypoemia	65.9% (31/47)	76.9% (10/13)
Mortality	4.2% (2/47) late	15.4% (2/13) early

TABLE III - Statistical evaluation of SAP-ESAP comparison

	SAP (47)	ESAP (13)	P
Impairment degree of pancreas	2,3	3,85	0,003
ACS	0/47 (0%)	1/13 (7,6%)	0,055
MOF	0/47 (0%)	6/13 (46,1%)	0,000
single organ dysfunction	24/47 (51,1%)	7/13 (53,8%)	0,859
Pancreatic sepsis	3/47 (6,3%)	3/13 (23,1%)	0,076
Hypoxemia	31/47 (65,9%)	10/13 (76,9%)	0,452
Mortality	2/47 (4,2%)	2/13 (15,4%)	0,155

Moreover in 225 cases (80%) out of our 276 patients with acute biliary pancreatitis, we performed ERCP/ES within 72 hours. This therapeutic procedure has been performed in the following cases: 60 patients (13 with ESAP and 47 with SAP); in 7 cases ERCP/ES was delayed for 10 days, and in 3 patients it was not possible; besides, in 73 patients with recurrent acute biliary pancreatitis; in 33 patients with moderate/severe acute pancreatitis; in 59 patients with mild/moderate AP with laboratoristic or US or MRCP confirmation of papillary or CBD lithiasis obstacle<sup>20</sup>. In 225 patients undergoing ERCP/ES, CBD cleaning was confirmed in 161 cases (71.5%). In the later phases of the disease the preferred approach to fluid and necrotic collections is US/CT guided percutaneous drainage, although on this point there are works in literature demonstrating the results of aggressive approach as we did in the past<sup>21-22</sup>. In our experience, considering 60 patients (47 with SAP and 13 with ESAP), we intervened only in 8 patients: 3 US/CT guided percutaneous drainage of infected necrotic collections, 2 US/CT guided percutaneous drainage of intrahepatic fluid collections, 2 laparotomies with necrosectomy and drainage, 1 open approach for ACS.

## Discussion

AP is an inflammatory process of the pancreas with possible peri-pancreatic tissue and multi-organ involvement inducing MODS with an increased mortality rate<sup>2</sup>. Biliary lithiasis is the most frequent cause of acute pancreatitis because of the obstruction to the bile outflow. AP is not a stable disease, but it has different clinical features for severity and evolution. The majority of patients present with a mild/moderate disease; however approximately 20-30% run a severe course and require appropriate management in intensive care unit. SAP can be seen as a biphasic disease, with the first two weeks phase characterized by early toxic-enzymatic injury (SIRS, MODS) and a later phase in the third and fourth week characterized by septic complications (infection of necrotic tissue and of peri-pancreatic fluid collections)<sup>23,24</sup>. Pancreatitis can present different severity in the first (toxic) phase: it can be self-limiting or quickly responsive to intensive care (especially rehydration), or it can quickly evolve in SIRS and multi-organ failure (MOF)<sup>25</sup>. In a new nosographic approach AP has a broad spectrum of clinical manifestations. The most important changes in the clinical picture come from two elements: possible organ failure and complications of pancreatic and peri-pancreatic necrotic collections<sup>26,27</sup>. It is possible to identify four clinical manifestations of AP: Mild: no complications of pancreatic/peri-pancreatic collections, no organ failure; Moderate: sterile pancreatic/peri-pancreatic complications or transient organ failure; Severe: pancreatic/peri-pancreatic complications or persistent organ failure; Critical: pancreatic/peri-pancreatic complications and persistent organ failure. The response of the pancreatic tissue to an injury, like acinar cells necrosis, leads to production and liberation of proinflammatory cytokines, chemokines and other biological active compounds<sup>1,28-31</sup>. Clinical and experimental studies have shown activation of local macrophages and attraction of activated polymorphonuclear cells as first-line players in the defense and limitation of pancreatic tissue injury<sup>1,32-34</sup>. Inflammatory mediators, such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), platelets activating factor (PAF) and tumor necrosis factor (TNF), are primarily released from the splanchnic area and gain access to the systemic compartment mainly by lymphatics, portal vein and suprahepatic circulation<sup>1,28-35</sup>. Gut barrier failure, with the ensuing translocation of bacteria and endotoxin, has been proposed as a major contributor to the development of local infection and multi-organ failure in SAP<sup>1,36</sup>. Intestinal permeability disturbances have been found in humans with SAP 72 hours after onset, correlating strongly with clinical outcome<sup>1,37</sup>. The peritoneal compartment is the site of pro-inflammatory reaction to pancreatic necrosis, whereas an anti-inflammatory response dominates in the lymph collected from the thoracic duct, as well as in the systemic complications<sup>1,28-29</sup>. In SAP a compensatory anti-inflam-

matory response affects the immunocompetence<sup>1,38-39</sup>. In summary ESAP can develop by altered balance between pro-inflammatory reaction to pancreatic necrosis in the peritoneal compartment (positive effect) and systemic circulation and diffusion of high level of anti-inflammatory mediators (negative effect leading to SIRS and MODS). Early mortality in the first week of ESAP is due to SIRS with early multi-organ insufficiency syndrome<sup>1,40</sup>. The early correct evaluation of pancreatitis severity has been a pressing clinical need for a long time. Numerous predictive factors of pancreatitis severity have been proposed and used: markers in blood and urine, multifactorial bioclinical scores, morphological exams. Predictive factors of severity, besides clinical examination, can be divided in direct and indirect. The first are morphological and evaluate pancreas anatomical impairment by means of imaging techniques (US, CT, MR). They provide a precise image of the organ impairment but they require an interval of time (24-48 hours) from the onset of the disease for the lesions to develop. The CT severity index (Balthazar) is based on imaging. The indirect methods, divided in mono-factorial and multi-factorial, consist, among the first, of all the blood, urinary and biochemical indexes which can be considered early detectors of systemic inflammatory response and of multi-organ dysfunction. Multi-factorial bioclinical scores specific for pancreatitis, Ranson, Glasgow and the non-specific score APACHE II (Acute Physiology And Chronic Health Evaluation) allow to correctly classify the great majority of acute pancreatitis (about 80%) only among the moderate and high severity forms. This distinction is rather generic because, as it is possible to evince from this experience and especially from numerous and recent data in literature, among severe pancreatitis, at least two different degrees of impairment of the clinical conditions can be identified. The immediate prevision, based on clinical observation and on laboratory and instrumental data present at the moment of hospitalization, is not completely reliable if limited to a single evaluation. Infact Ranson and Glasgow scores require a re-evaluation after 48 hours. Also APACHE II score, even if applicable since the first observation, is nonetheless based on clinical evolution data. A great amount of studies have been developed with the aim of evaluating biochemical factors which manifest or alter themselves when the general inflammatory reaction starts and thus the multi-organ impairment, central element of severe acute pancreatitis<sup>41</sup>. Among uni-factorial prognostic factors particularly evident for their precocity and reliability and objects of many studies, are C-reactive protein (CRP), the urinary level of tissue plasminogen activator (TPA) and pro-inflammatory and anti-inflammatory cytokines. In the general scheme of predictive factors of severe evolution we can distinguish the factors assessed at the onset of the disease or within few hours and on the other hand predictive markers of poor outcome assessed when the clinical picture has become severe. The

results of the comparison between our two groups of patients, severe and more severe pancreatitis, have shown that the distinction is actual and useful. In fact, in the first phase of the disease (1-2 weeks), pancreas pathological alteration (CT severity index), multi-organ dysfunction and compartment syndrome are in evidence as discriminant data between severe and critical forms. In a late phase of pancreatitis evolution the septic complication of pancreatic and peri-pancreatic necrotic fluid collections assumes a discriminant role, even if in our study it is at the limit of statistical significance. Our experience, even if numerically very limited, shows that it is possible to identify within SAP clinical forms of particular severity. However, the clinical features which cause a pancreatitis to become very severe present a temporal sequence: in the first phase, the multi-organ impairment, while in a following phase the septic complication of the fluid collections, which is however possible also in the less severe forms where multi-organ dysfunction was at the beginning absent or transient. According to our data the difference in mortality incidence between the two groups of patients (SAP and ESAP), even if evident, is not statistically significant ( $p=0.155$ ). From a detailed analysis of our experience it is possible to notice that, in the group classified as critical, mortality is present in the initial phases when the most evident clinical aspect is represented by ACS and MODS which are the cause of death. On the contrary, mortality in the SAP group is present in the late phase and is connected to the septic complication which intervenes after the organ dysfunction has been controlled. Thus, according to the data gathered with our analysis, even if within the limits deriving from schematizations, two phases in the evolution of SAP can be detected. The first phase, which can be limited to the 1st-2nd week from the onset in which severity is graduated by general conditions impairment: transient or stable organ or multi-organ dysfunction to the severe complication of abdominal compartment syndrome. Thus early mortality is linked to the severity of the systemic inflammatory syndrome. The extension and the degree of phlogistic-necrotic involvement of the pancreas and peri-pancreatic space, even if remaining an index of severity, does not seem to have a directly proportional relationship with multi-organ dysfunction (number of organs, transient or persistent dysfunction). Persistent dysfunction may worsen the extension of pancreatic necrosis because of reduced perfusion<sup>42</sup>. Thus the connection between necrosis and organ failure, which are not necessarily correlated<sup>43</sup>, is not clear.

Therapeutic approach in the first phase tries to control and treat general complications, i.e. systemic inflammation response syndrome (SIRS) and MODS, applying intensive care, preserving intestinal wall integrity and assuring papillary patency in biliary pancreatitis. First intensive care consists of fluid replacement, including colloids, to achieve isovolemic hemodilution and organ sup-



port<sup>44-45</sup>. In systemic inflammation several pro-inflammatory cytokines activate the coagulation process in the body and activate endothelial cells<sup>46</sup>. Systemic coagulation activation results in thrombosis in small and middle-sized vessels in many organs, resulting in disseminated intravascular coagulation (DIC). So anticoagulant agents and recombinant activated protein C can be given.<sup>47-48</sup> Also low dose steroids and intensive insulin treatment, if there is hyperglycemia >200mg/dl, may be necessary. Antibiotic prophylaxis and enteral feeding reduce significantly the infection rate of necrosis<sup>1,49-52</sup>. The second, late phase is in the 3rd-4th week and beyond. It is characterized by the evolution of pancreatic and peri-pancreatic fluid-necrotic collections, resulting from the self-digesting inflammatory process. The collections may be reabsorbed generally over a long time or in infrequent cases (15%) they may cause the formation of post-necrotic pseudo-cysts. The most severe event is represented by the collections infection. In the literature has been reported also cases of aneurysm in course of acute pancreatitis<sup>53</sup>. So the septic complication characterizes the severity in the late phase of acute pancreatitis. The evacuation with US-CT guided percutaneous drainage of fluid-necrotic collections and of possibly infected collections represents the therapeutic standard. The new nosographic formulation proposed by Petrov<sup>26</sup> which identifies an increasing severity on the basis of the presence of transient or stable organ dysfunction and of septic complication of pancreatic and peri-pancreatic post-necrotic collections can be integrated by the temporal clarification of the two clinical elements of severity which generally are not simultaneous. In our opinion it is necessary to clarify that there are critical or early severe acute pancreatitis characterized in the initial phase by SIRS with multi-organ dysfunction and equally severe forms in the late phase, after resolution or at least control of MODS which are instead characterized by septic complication of fluid-necrotic collections. Moreover, the septic complication can develop after some time (3-4 weeks). In fact fluid-necrotic collections may be considered the result of the pancreatic phlogistic process on which subsequently the septic complication, generally for bacteria translocation, superimposes.

## Conclusion

Compared to SAP, ESAP is characterized, in a first phase, by early major and serious involvement of general conditions (SIRS, MOF). In ESAP there is a major incidence of ACS, MODS, high degree of pancreatic impairment. In patients with ESAP, longer intensive therapy and hospitalization are necessary. In a later phase the gravity of severe pancreatitis depends on the septic complications of fluid necrotic collections. In ESAP the incidence of mortality is higher than in SAP (15.4%) because of multiorgan dysfunction (in the first phase). In SAP

the incidence of mortality is 4.3% because of septic complications (in the later phase). Severe forms are less represented in biliary pancreatitis. Treatment of SAP and ESAP is now more conservative and less invasive than in the past and it is based on: intensive care, prevention of intestinal failure and maintenance of papillary patency in the first phase of the disease, also for the prevention of recurrent pancreatitis<sup>54</sup>. In the later phase the therapeutic procedure, if there are pancreatic and peri-pancreatic fluid necrotic collections, is US/CT percutaneous catheter drainage.

## Riassunto

La pancreatite acuta severa (SAP) è caratterizzata da gradi diversi di gravità. L'obiettivo di questo studio è di identificare, nell'ambito delle SAP, forme critiche (ESAP) di particolare gravità. Durante il periodo 1997-2011 sono stati trattati 276 pazienti affetti da pancreatite acuta, tutte con eziopatogenesi biliare nella nostra esperienza. L'incidenza di SAP è stata del 21.7% (60), e fra queste abbiamo osservato 13 pazienti con ESAP, caratterizzata dalla comparsa di disfunzione d'organo entro le 72 ore dall'inizio dei sintomi. Abbiamo valutato i diversi quadri clinici, il tipo di disfunzione singola d'organo e le scelte terapeutiche nei due gruppi: pazienti con SAP (47) e pazienti con forme cliniche critiche (ESAP) (13). La valutazione dei dati riguardanti i due gruppi ha fornito questi risultati: grado di coinvolgimento del pancreas (Balthasar score) è stato di 2.3 in SAP vs 3.85 in ESAP, la sindrome compartimentale addominale è stata riscontrata in 1 solo paziente con ESAP (7.5%), sindrome da disfunzione multi organo (MODS) in 6 pazienti con ESAP (46.1%), disfunzione singola d'organo in 24 pazienti con SAP (51%) e 7 con ESAP (53.8%), stato settico in 3 pazienti con SAP (6.3%) e 3 pazienti con ESAP (23%), ipossiemia in 31 pazienti con SAP (65.9%) e 10 pazienti con ESAP (76.9%). Il tasso di mortalità è stato di 4.34% nelle SAP e 15.4% nelle ESAP. Nell'ESAP l'incidenza di MODS, sindrome addominale compartimentale e grado di coinvolgimento del pancreas è maggiore. Nell'ESAP il tasso di mortalità è maggiore: 15.4% ed è legato alla disfunzione multi organo mentre nelle SAP è di 4.3% per via delle complicanze settiche in fase tardiva. Il trattamento dei pazienti con SAP ed ESAP attualmente è più conservativo e meno invasivo rispetto al passato: inizialmente sono necessarie la terapia intensiva e assicurare la pervietà papillare. Successivamente il trattamento delle raccolte fluide necrotiche è il drenaggio percutaneo.

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