

Clinical Importance of the Determinant-Based Classification of Acute Pancreatitis Severity

D. Cochior¹, S. Constantinoiu², C. Copăescu³, D. Șerbănoiu⁴, R. Bîrlă², M. Boeriu⁵

¹"Titu Maiorescu" University, Department of Surgical Disciplines, Faculty of Medicine, Surgical Department Hospital CF 2 Bucharest, Romania

²UMF "Carol Davila", Department for General and Esophageal Surgery "St. Mary" Hospital, Bucharest, Romania

³Delta Hospital, Bariatric Center of Excellence, Bucharest, Romania

⁴Surgical Department Hospital CF 2, Bucharest, Romania

⁵Department for General and Esophageal Surgery "St. Mary" Hospital, Bucharest, Romania

Rezumat

Importanța clinică a clasificării pancreatitei acute pe baza factorilor determinanți

Scop: Această clasificare ar trebui să elimine confuziile din terminologie apărute în ultimii 20 de ani cu implicații directe în practica clinică.

Metodă: Studiul a avut la bază consultarea pe web a specialiștilor la nivel mondial. Au fost trimise 528 de invitații și au fost primite 240 de răspunsuri din 49 de țări reprezentând toate continentele.

Rezultate: În încercarea de a elimina majoritatea confuziilor vechii clasificări au fost emise definiții ce au încorporat conceptele moderne ale bolii, s-a îmbunătățit evaluarea clinică a severității pe baza factorilor determinanți locali și sistemici, s-au creat premisele unei raportări de date standardizate.

Critici: O clasificare ideală ar trebui să reflecte întregul tablou al modificărilor clinico-paraclinice ale unui pacient, la un moment dat. În clasificarea adoptată, variabila principală ce caracterizează gradul severității este numai disfuncția de organe tranzitorie sau persistentă.

Concluzii: Cea mai importantă contribuție este redefinirea complicațiilor locale bazate pe conținutul acestora, existența sau inexistența peretelui, locul de apariție și evoluția acestora în timp (factori determinanți locali). Factorii determinanți sistemici iau în considerare prezența disfuncțiilor de organ (tranzitorii sau persistente). Prezența factorilor determinanți are un efect cumulativ, se pot influența reciproc iar infecția poate apare la toate cele patru tipuri de leziuni.

Cuvinte cheie: clasificare, severitate, pancreatita, colecții fluide acute, necroza pancreatică sau peripancreatică, necroza încapsulată/inchistată

Abstract

Purpose: This classification should eliminate the confusion in terminology occurring over the last 20 years with direct implications in clinical practice.

Method: The study was based on the web-based consultation of experts worldwide. 528 invitations were sent and 240 responses received from 49 countries from all continents.

Results: In an attempt to eliminate many confusions of the old classification, definitions that have built-in modern concepts of the disease have been issued, clinical evaluation of the severity has been improved and a standardized reporting data to objectively evaluate new treatments and to facilitate the communication of data between centers has been created.

Discussions: An ideal classification should reflect the whole area of clinical and paraclinical changes for one patient, at a given time. In the chosen classification, the main variable that characterizes the degree of severity is only the transitory or persistent organ dysfunction(s)/failure(s).

Corresponding author:

Daniel Cochior, MD, PhD
Principal Investigator I
„Titu Maiorescu” University
Surgical Disciplines Department
Faculty of Medicine
Surgical Department Hospital CF 2
Mărăști Avenue, 63, sector 1, 011464,
Bucharest, Romania
E-mail: cochiordaniel@gmail.com

Conclusions: The most significant contribution to this update is redefining local complications based on their content, existence or non-existence of the wall, the place of their appearance and their evolution over time (local determinants). Systemic determinants take into account the presence of organ failures (transient or persistent). The presence of determinant factors has a cumulative effect.

Key words: severity, pancreatitis, acute fluid collections, pancreatic or peripancreatic necrosis, walled-off necrosis

Introduction

We can say that the apparent downward trend in mortality in acute pancreatitis in the last 20 years emphasizes the progress made in the management of this disease. However, despite the many aspects of the pathophysiology of the disease (1,2), clinical and laboratory severity ranking is quite ambiguous, based on empirical description of clinical changes and the simplistic Atlanta classification (1992), without net demarcation or clear definitions, hampering multicenter trials, resulting in suboptimal assessment (3,4). When errors of interpretation and understanding are found in a significant percentage of such studies, it is natural that the results are compromised (3). Although not intended to be a guide with therapeutic implications, the purpose of this document is to present the new classification of severity of acute pancreatitis and to highlight the value applied in medical practice.

History

The first attempt to classify the severity of acute pancreatitis belongs to Fitz in 1889, and until the Atlanta classification (1992), a morphological component was always included (5,6). If according to Fitz's conception, severe disease characteristic morphology is represented by diffuse hemorrhage and disseminated fat necrosis, the Atlanta morphological features of severity are represented by pancreatic necrosis, abscess and pancreatic/peripancreatic pseudocyst. Subsequently, as stated by Petrov (7), there is an ongoing effort to revise the Atlanta criteria in the light of new clinical and laboratory evidence. In 2012 the classification was updated, by consensus, taking into account local and systemic determinants of the disease (8). Determinants approach provides a concise set of updated definitions, useful both in clinical practice (acute pancreatitis severity classification for classification of patients into risk groups) and in research aimed at using them in the same manner all over in the world. Although some groups have suggested a hierarchy of severity in 2 (medium and severe) or 4 degrees (average, moderate, severe and critical - in our opinion more adequate for teaching and clinical research) (4,9,10), this last version with 3 degrees of severity, defined by risk groups (morbidity and mortality) seems to be easier in medical practice (8,11,12,13).

Method

The study was based on articles published in the field and the world's experts were consulted; authors who have published articles on acute pancreatitis in the last 5 years were invited (surgeons, gastroenterologists, internists, anaesthesiologists and intensive care specialists, radiologists etc). 528 invitations were sent and 240 responses received from 49 countries from all continents (9). The leading author of this article has accepted the invitation of Professor Dellinger EP (Washington University, Seattle, USA) to participate in this survey (4). Thus, Atlanta classification was considered appropriate for modern clinical practice by only 40 (17%) of respondents. The determinants-based approach to classifying the severity of acute pancreatitis was considered appropriate for modern clinical practice by 188 (78%) of respondents and for clinical research by 191 (80%) of respondents. As a result, classifying the severity of acute pancreatitis on the Atlanta scale was considered inappropriate by most respondents, thus resulting the need for an international consensus (2012), considering the results of this survey (7,10). New classification clarifies local and systemic determinants of severity. Local determinants take into account the presence or absence of pancreatic or peripancreatic necrosis and, also, if there is necrosis, its quality: sterile or infected. Systemic determinants are considering the absence or presence of organ dysfunction /failures, transient or persistent (12). Determinants presence has a cumulative effect, they can influence each other: the presence of infected pancreatic and peripancreatic necrosis associated with persistent organ dysfunction has a much stronger effect on the severity (7).

Revised definitions

The following definitions and classifications are proposed for use in clinical practice and research. To facilitate understanding, each local complication has eloquent tomographic images.

Definition of acute pancreatitis

The diagnosis of acute pancreatitis requires at least 2 of the following 3 features: abdominal pain (epigastric pain often radiating to the back and in the left flank), serum amylase and lipase levels at least three times greater than the upper limit of normal and characteristic findings on contrast-enhanced CT, magnetic resonance (MR) imaging or transabdominal ultrasonography (US) (12). Sometimes the CT examination is essential to confirm the diagnosis: abdominal pain suggestive for the disease but without serum amylase and lipase levels at least three times greater than the upper limit of normal, as it happens in late presentation of the patient. If acute pancreatitis is diagnosed on the basis of the first two criteria, contrast-enhanced CT may not be necessary in emergency (13,14).

Definition of onset of acute pancreatitis

The onset of acute pancreatitis is defined as the time of onset of abdominal pain; this is not the same with the time

of admission to the hospital. The interval between onset of abdominal pain and admission to the hospital should be noted precisely, especially if patients with severe pancreatitis are transferred to a specialised care unit (second admission) when this type of data are often neglected (12,13,14).

Definition of the types of acute pancreatitis

There are two types of acute pancreatitis: interstitial edematous pancreatitis and necrotizing pancreatitis. Interstitial edematous acute pancreatitis (IEP) appears mostly as a diffuse enlargement of the pancreas due to inflammatory edema and, very rarely, is located only in a part of the pancreas (13). Contrast-enhanced computed tomography shows local or diffuse enlargement of the pancreas with homogeneous or slightly heterogeneous contrast of the pancreatic parenchyma due to edema (Fig. 1). Peripancreatic and retroperitoneal tissue may look normal (at the beginning) or inflammatory type changes can be observed in the peripancreatic tissue, appearing "blurry" or with different amounts of peripancreatic liquid. A few days after onset, the heterogeneous areas in the pancreas may increase in size and at this stage, the appearance could not be definitively characterized as IEP or patchy necrosis (Fig. 2). Therefore, computed tomography performed after 5-7 days will allow a clear evaluation of local complications (15).

There are three forms of necrotizing pancreatitis, depending on location, and all can be sterile or infected. Necrotizing pancreatitis usually occurs both in the pancreas and peripancreatic, sometimes only peripancreatic and rarely only pancreatic (13). Pancreatic parenchymal necrosis alone can be seen in less than 5% of patients and appears on contrast-enhanced CT images as lack of parenchymal enhancement (12), because the nonviable and necrotic tissues slowly begin to liquefy. The extent of parenchymal necrosis is divided into two categories: less than and greater than 30% of the gland involved (three categories according to Atlanta classification: less than 30%, 30%–50%, greater than 50%)(13,15). At times, areas of no or poor enhancement that are estimated to be less than 30% in the early phase may actually be findings of edema rather than necrosis (15) (Fig. 3). Peripancreatic necrosis alone can be seen in approximately 20% of patients and can be difficult to confirm (15,16,17) (Fig. 4). The presence is diagnosed when heterogeneous areas of non-enhancement are visualized containing solid components. Peripancreatic necrosis is commonly located in the retroperitoneum and lesser sac. The clinical importance of peripancreatic necrosis alone lies in the fact that patients with this condition have a better prognosis than patients with pancreatic parenchymal necrosis do (16), but they have a higher morbidity rate and a higher rate of surgical interventions (17,18). Pancreatic parenchymal necrosis with peripancreatic necrosis is the most common type and can be seen in 75-80% of patients (12,14). Radiological changes found are a combination of the two forms of necrosis descriptions showed above (Fig. 5). In this case, the necrotic areas may be connected to the main pancreatic duct ("disconnected duct syndrome") (19,20). The affected pancreatic perfusion and peripancreatic necrosis can be revealed only after a few days of



Figure 1. Patient (MI) 54 years old with acute interstitial edematous pancreatitis. Pancreas increased in overall volume (asterisk), homogeneous opacified but embattled shape because of peripancreatic edema. Minimal peripancreatic acute fluid collections (white arrows) present in the tail and head of the pancreas



Figure 2. Contrast enhanced CT scan performed 48 hours after onset of acute non biliary pancreatitis in a patient of 43 years old (PC). Enlarged, heterogeneous pancreas, especially cephalic (arrows). In this stage can be defined as interstitial edematous pancreatitis or necrotizing pancreatitis (pancreatic necrosis?)

disease progression and, therefore, computed tomography performed at the onset of acute pancreatitis cannot predict what changes will occur, eg. extension of pancreatic and peripancreatic necrosis (15,21,22). After the first week of progression, the pancreatic heterogeneous areas of non-enhancement should be considered pancreatic necrosis. In peripancreatic necrosis, the pancreas may appear normal or like in interstitial edematous pancreatitis but with peripancreatic necrotic areas. The natural history of pancreatic and peripancreatic necrosis is variable: this can be solid or liquefied, it may remain sterile or become infected, it can persist or disappear over time (13,15).

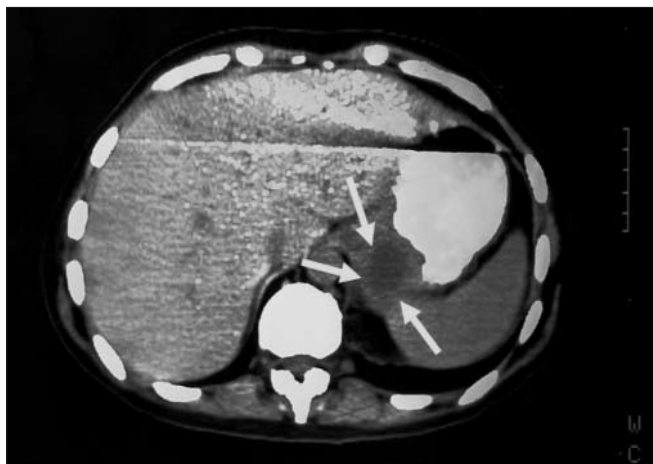


Figure 3. Female patient (ND) of 49 years old, with obesity and severe acute biliary pancreatitis. Single pancreatic necrosis: pancreatic tail larger in size, having a diameter of 5 cm with an area of necrosis inside of about 4 cm which also mark the gastric angle



Figure 4. Female patient (CT) of 38 years old with acute non biliary pancreatitis. Pancreas moderately enlarged, especially caudal. Single peripancreatic necrosis extended to the posterior pararenal left space and superior and anterior to the left colic angle and left recession of the lesser sac (omental bursa)

Infected necrosis

Generally, the clinical findings do not suggest a definite correlation between the extension of necrosis and the risk of infection (12). Diagnosis of infected pancreatic necrosis is directly reflected in the treatment plan (antibiotics and direct intervention on these areas: percutaneous drainage, interventional endoscopy, minimally invasive or classic surgery) (6,21-25). Infection of pancreatic necrosis in the first week of disease progression is very rare (12,13). Infected necrosis may be suspected in the presence of extraluminal gas bubbles (26,27) in the pancreatic tissue and/or peripancreatic on CT examination, in conjunction with clinical data (28) (Fig. 6). Spontaneous drainage of collections in the gastrointestinal tract can lead to erroneous suspicion of infected necrosis; this diagnostic error can be avoided by careful analysis of the gastrointestinal wall (15). Gas bubbles can also be present in collections after surgical procedures, like the marsupialisation of the lesser sac or after other drainage procedures (29,30). The definitive diagnosis of infected necrosis is made only by the positive bacterial or fungal cultures after CT guided fine needle aspiration (FNA) from areas of necrosis! (13,14). This procedure should be carried out only if there is a high clinical suspicion of infected necrosis, with all necessary precautions to avoid external contamination – the anterior transperitoneal path should be avoided (15); the preferred path is retroperitoneal, by lateral approach. If the result is negative (false negative in about 10% of cases) but clinical suspicion of infected necrosis persists, the bacteriological examination of cultures obtained by FNA should be repeated. Collections of pus and necrosis tend to increase over time through liquefaction. The Atlanta classification (5) defines localized purulent collections with quantita-

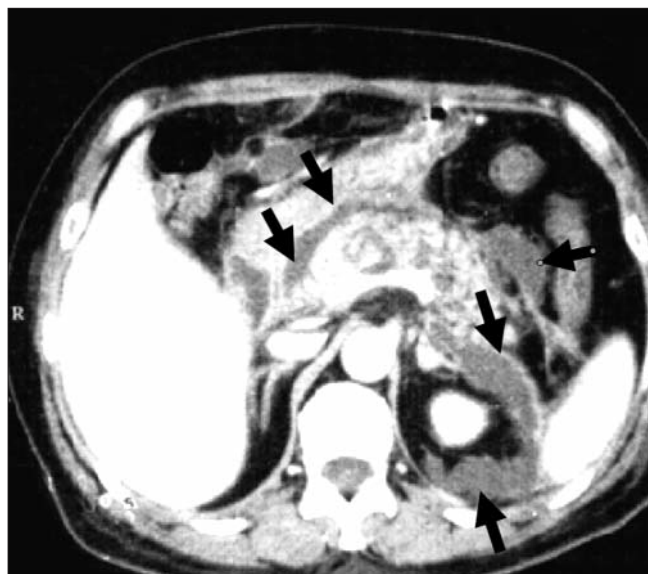


Figure 5. Female patient (NA) of 62 years old with severe acute biliary pancreatitis, 8 days after onset. Areas of necrosis in all the segments of the pancreas. Acute necrotic collections (white arrows) all around the pancreas, with extensions in transverse mesocolon and left pararenal space

tively insignificant necrosis with the term "pancreatic abscess". Because this is not a frequent lesion and the term is confusing, leaving room for interpretation, this terminology was not adopted by most clinicians and it no longer exists in the revised classification terminology (4,9). Infected necrosis is associated with increased morbidity and mortality (16).

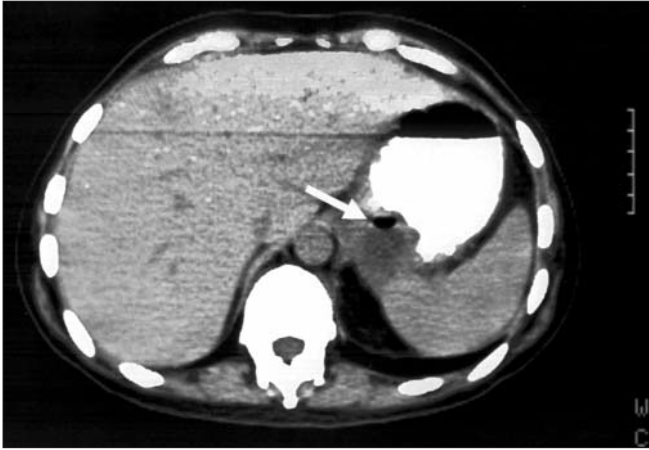


Figure 6. Female patient (ND) of 49 years old with obesity and severe acute biliary pancreatitis. Secluded necrotic collection (WON) after 4 weeks of evolution - "air-liquid level" inside. Basically, in this case there is no need for tomography-guided fine needle aspiration, because of the pathognomonic sign

Definition of organ dysfunction/failure (persistent or transient)

The most accurate marker in defining the severity of disease is dysfunction/persistent organ failure (lasting over 48 hours) (14,31). Three organ systems should be assessed to define organ failure: respiratory, cardiovascular and renal. Persistent organ failure is defined with the modified Marshall scoring system as a score of at least 2 or for at least one of these three organ systems (32). Transient organ failure is important in defining the moderately severe form of acute pancreatitis and assumes a score of at least 2 or for at least one of these three organ systems, but for less than 48 hours (Table 1). This score was chosen for its simplicity, universal applicability in clinical practice and in research and its ability to stratify disease severity easily (12). This score is preferred comparing to other scores and it can be recalculated over time for reassessing the

severity of the disease. Other scoring systems, such as the SOFA scoring system and APACHE II for patients managed in a critical care unit, which includes inotropic and respiratory support, can be determined to assess the severity of dysfunction/organ failures. However, for an easier hierarchy, these scores are not included in current classification (12,14).

Definition of local complications

The presence or absence of local complications is very important. Local complications of acute pancreatitis are: acute peripancreatic fluid collections, acute necrotic collections, pancreatic pseudocyst and walled off necrosis (12-15). Other local complications of acute pancreatitis include perturbation of gastric emptying, splenic or portal vein thrombosis, necrosis of the colon (13,22). Local complications may be suspected in the presence of recurrent or persistent abdominal pain, increased serum enzymes, worsening of the organ dysfunction and/or clinical signs of sepsis (fever or leukocytosis) that require imaging evaluation (29,30,33). The contrast enhanced computed tomography (CECT) was able to describe objectively, accurately the characteristics of local complications. To make an accurate diagnosis, in describing these complications, the location (pancreatic, peripancreatic etc), the content (liquid, solid, gaseous), the existence of a wall around the collections or necrosis (thin or course) and perfusion (normal or poor) of the pancreatic gland should be highlighted (15).

Definition of pancreatic and peripancreatic collections

The revised classification makes a clear distinction between collections containing only fluid as compared to those formed of tissue necrosis (solid component) and varying amounts of fluid (Table 2). Local complications are defined by objective criteria (local determinants) based mainly on computerized tomography with non-ionic contrast (15). These complications are: acute peripancreatic fluid collections (APFC), pseudocyst (rarely found in acute pancreatitis), acute pancreatic/

Table 1. Modified Marshall Scoring System for organ failure (32)

System	SCORE				
	0	1	2	3	4
Respiratory (PaO ₂ /FiO ₂)	>400	301-400	201-300	101-200	≤101
Renal* (Serum creatinine, mg/dl)	≤1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg, without inotropic support)	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2
For non-ventilated patients, the FiO ₂ can be calculated from below:					
	supplemental oxygen (l/min)		FiO ₂ (%)		
	room air		21		
	2		25		
	4		30		
	6-8		40		
	9-10		50		

A score equal to or greater than 2 of each system defines the presence of organ failure

* In patients with chronic renal failure, the score depends on the degree of renal function deterioration.

peripancreatic necrotic collection (ANC) and walled off necrosis (WON) (12-15). All of the 4 types of collections can be sterile or infected. Collections containing preponderant solid material are more likely to become infected (14,27). The distinction between sterile and infected collections is important because both treatment and prognosis are different. Cases with infected necrosis, for example, require intervention by percutaneous drainage, endoscopic, laparoscopic or surgical interventions (21,26,34-36). Sterile necrosis does not require surgery until persistent pain occurs, anorexia, vomiting or inability to resume oral nutrition in more than 4 weeks after onset (21,26,29). This classification will help clinicians to predict outcome in patients with acute pancreatitis (risk groups of morbidity and mortality) and allow comparison of patients and treatment/management of the disease in various centers and locations around the world (9).

Acute peripancreatic fluid collections arise in patients with interstitial acute edematous pancreatitis, are predominantly adjacent to the pancreas, fluid and have no definable wall. These occur in the first 4 weeks from the onset of the disease, and are confined by the normal peripancreatic fascial planes of the retroperitoneum, primarily the anterior pararenal fascia (Fig. 7). Usually these are not infected and need no surgical intervention because they are not associated with pancreatic necrosis (12-15). If these collections last over four weeks they will probably evolve to pancreatic pseudocyst, although a true pseudocyst (a persistent fluid collection surrounded by a well-defined wall containing no solid material) is rare in acute pancreatitis. Drainage or aspiration of these collections (except of infected pseudocysts) is forbidden because they may be contaminated from the outside.

Acute necrotic collections occur in necrotizing pancreatitis and can be intra- or extrapancreatic, single or multiple, heterogeneous, with solid (necrotic) and fluid content in varying proportions and without a clear encapsulation. Their content is a spectrum ranging from predominantly necrotic (solid) to both fluid and necrotic material. These occur in the first 4 weeks of progression of the disease. The necrosis involves the pancreatic parenchyma or peripancreatic tissues. These collections may be associated with disruptions of the pancreatic duct within parenchymal necrosis and can get infected (12-15) (Fig. 8). Development of a pancreatic pseudocyst in the evolution of acute pancreatitis is very rare and



Figure 7. Acute peripancreatic fluid collections extended to transverse mesocolon, lesser sac and pararenal spaces (arrows) in a patient (PI) with acute interstitial edematous non biliary pancreatitis

should be stressed that this is not the evolution of an acute necrotic collection (14). The terminology of pancreatic pseudocyst must be used specifically only for a peripancreatic fluid collection, and very rarely intrapancreatic, with a well-defined wall and insignificant percentage of solid residue, which occurs after more than 4 weeks in the progress of acute pancreatitis (15) (Fig. 9). The pathogenesis of the pancreatic pseudocyst is explained by the occurrence of injury to the pancreatic ductal system in the absence of pancreatic/peripancreatic necrosis (solid material) showed by imaging methods (ultrasonography, CECT or MRI). When the ultrasonography, CECT or MRI is showing solid, necrotic material in a cavity containing fluid, the term "pancreatic pseudocyst" should not be used (13,15) (Fig. 10).

Walled off necrosis – WON develops only in acute necrotizing pancreatitis, can appear in pancreatic parenchyma or peripancreatic tissues, can be heterogeneous with solid content (necrosis) and fluid in varying proportions within a wall which encloses it, made of inflammatory tissue (12-15). Occurring in

Table 2. New classification of collections in acute pancreatitis (13)

Time from onset	Form of pancreatitis	Fluid collections		
< 4 weeks of progression Acute complications	Interstitial edematous	Acute peripancreatic fluid collections		Sterile infected
		Only pancreatic parenchyma necrosis		Sterile infected
	Necrotic	Only peripancreatic necrosis		Sterile infected
		Pancreatic necrosis associated with peripancreatic necrosis		Sterile infected
≥4 weeks of progression	Interstitial edematous	Pancreatic pseudocyst		Sterile infected
Chronic complications	Necrotic	Walled off necrosis		Sterile infected

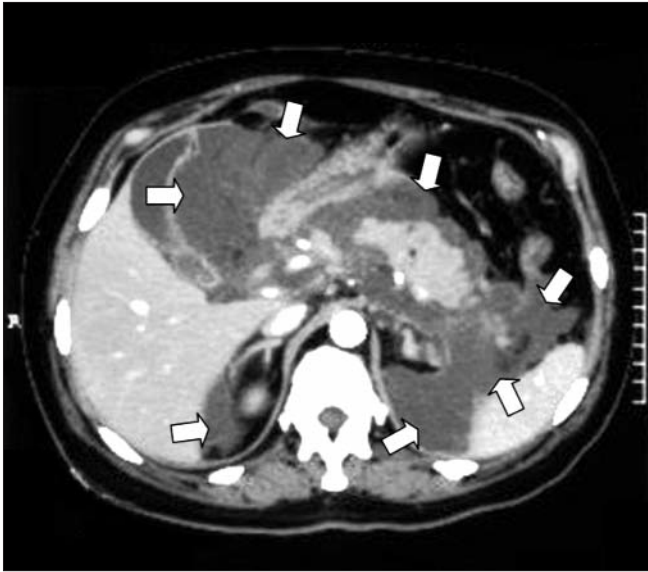


Figure 8. Female patient (PM) of 45 years old with severe acute biliary pancreatitis. Pancreas with edema and necrotic areas in all pancreatic segments. Liquid collections all around the pancreas, with extensions in: lesser sac, mesocolon, bilateral pararenal, perisplenic

more than 4 weeks after the onset of acute pancreatitis, the collections are made of pancreatic or peripancreatic necrosis, encapsulated, with a well-defined inflammatory wall (Fig. 10, 11). These collections are mentioned in literature with various inappropriate names: organized pancreatic necrosis, pancreatic seizures, pseudocyst associated necrosis, subacute pancreatic necrosis, etc (12). WON can be infected and sometimes found away from the pancreatic gland. This collection is the most suitable for laparoscopic approach (depending on the location and surgical indication).

Definition of systemic complications

Systemic complications define the enhancement of any pre-existing comorbidity, such as coronopathies, chronic pulmonary disease, hepatic or renal disease, diabetes Mellitus, systemic inflammatory response syndrome (SIRS) that accompany the acute pancreatitis event. We must differentiate between persistent organ failures (as an effect of the disease severity) and these systemic complications that represent the enhancement of preexisting comorbidities (12-15).

Stages of acute pancreatitis

The reviewed classification identifies two stages in the development of acute pancreatitis, corresponding to two mortality peaks: early stage (first 7-14 days, through systemic inflammatory response syndrome – SIRS, and early MODS/MSOF) and late stage (2-6 weeks of development, through compensatory anti-inflammatory syndrome - CARS, intestinal bacterial translocation, infected pancreatic and peripancreatic collections, late MODS/MSOF) (12-15) (Fig. 12).

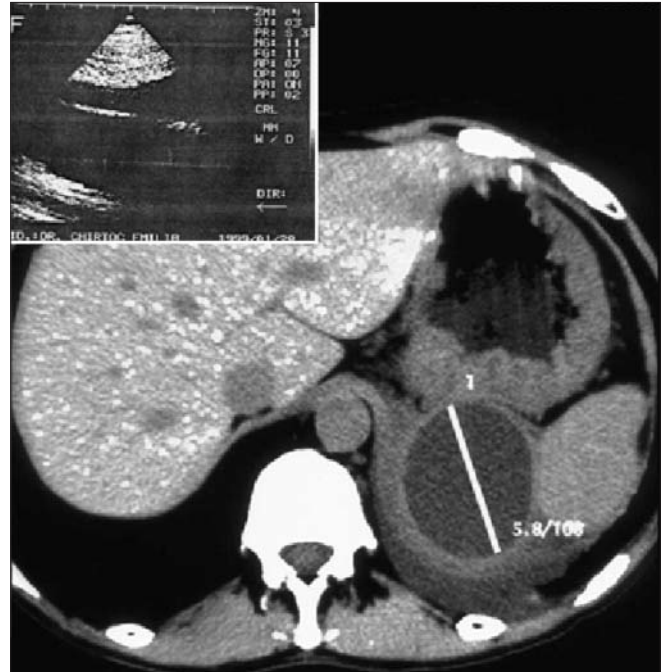


Figure 9. Male patient (NC) with moderately severe acute biliary pancreatitis, 8 weeks after onset. Unilocular cystic formation without calcification, iodophilic, liquid, homogeneous, without solid components, 60/110 mm in size, thick iodophilic wall, developed cranial of the pancreas body to lesser sac. Ultrasound (box): containing fluid, homogeneous, "water-like"

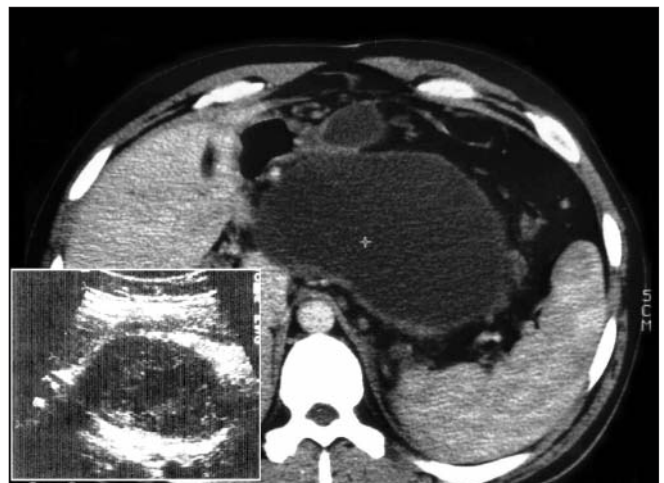


Figure 10. Sequestered necrosis (WON) interpreted as "pancreatic pseudocyst" in a male patient (AC) with severe acute pancreatitis, 4 weeks after onset. Ultrasound (box): giant heterogeneous sequestered collection, mixed content. Intraoperative is found a mixed collection: pus, pancreatic and peripancreatic necrosis

In the early stage, systemic events are determined by the host response to the cytokine cascades, manifested as a SIRS. When these events persist, organ dysfunctions become obvious. In this stage, the severity of the acute pancreatitis

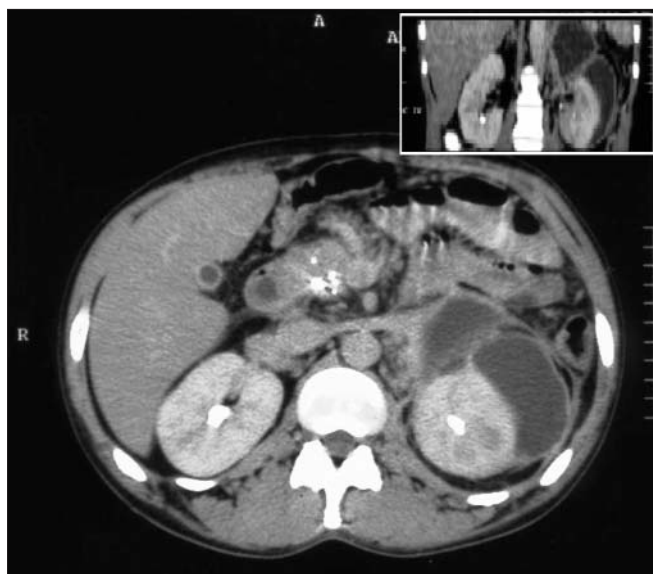


Figure 11. Male patient (DI) of 35 years old with severe acute pancreatitis, 5 weeks after onset (cross section). Cephalo-pancreatic necrosis of 15/15 mm (circle). Secluded necrosis in the left recess of lesser sac, 50/70 mm and left pararenal 50/120 mm (arrows). Homogeneous content, solid-liquid different densities. On sagittal section (box) we can notice the compressed left kidney due to the pararenal collection

event is defined by the presence and duration of the organ dysfunction: transitory (under 48 hours) or persistent (over 48 hours). When the dysfunction involves more than one organ, the term "multiple organ dysfunction/failure" (MODS/MOSF) must be used. Although local complications can be identified in the early stage, they cannot be used as determining factors in the severity, as it is difficult to mark the extent of collections and necroses after a few days of development (38). More so, the morphological changes discovered in this stage do not correlate with the organ dysfunction degree of severity (12,38). Thus, defining a pancreatitis as moderately-severe in the early stage depends most of all on the presence and duration of organ dysfunctions/failures (Table 3) (37,39). The late stage of acute pancreatitis, that can persist for weeks, even months, is characterized by the persistence of systemic signs of SIRS or as CARS that predisposes to infections (12,38,41), local and systemic complications and/or transitory or persistent organ dysfunctions/failures. This stage defines moderately-severe or severe acute pancreatitis. It is very important to distinguish, through imagery, the specific morphological features of every local complication because they directly influence therapeutic management (15,22,33,37,42). The persistence of organ dysfunctions remains the determining severity factor, even though both clinical and local morphological criteria are needed for characterizing this stage (2,13).

Ranking of acute pancreatitis severity

The disease's severity ranking defines three developmental

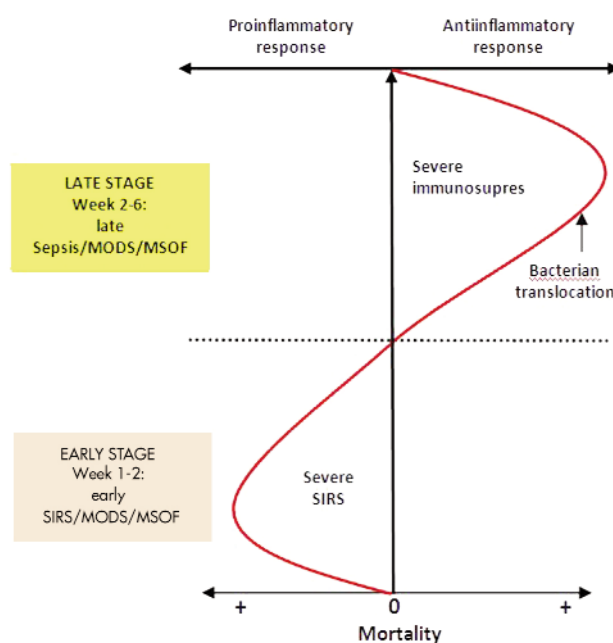


Figure 12. Acute pancreatitis stages

levels: medium form, moderately-severe form and severe form (Table 4) (12-15). The most frequent medium form, does not involve organ dysfunctions (in the modified Marshall score system) and local or systemic complications, and it often relegates in the first week of development. The moderately-severe form is defined by the presence of transitory organ dysfunctions (lasting less than 48 hours), local complications and/or the enhancement of current comorbidities. Morbidity is greater than mortality ($<8\%$) as compared to the medium form, but not as great as in the severe form. Patients are frequently discharged in the 2nd or 3rd week of hospitalization because of local or systemic complications (39,40). The severe form is defined by the presence of persistent (>48 hours) organ dysfunctions/failures. Local complications are represented by peripancreatic fluid collections, pancreatic or peripancreatic necrosis (sterile or infected). Patients that develop severe forms from the early stage of the pancreatitis have a high mortality rate (30-50%) (13,31,43). An infected necrosis enhances the risk of death (21,27,37).

Clinical implications

An important clinical implication is the acknowledgement of the fact that acute pancreatitis is a dynamic, evolving disease

Table 3. SIRS defined by the presence of one or more criteria: (12-15)

Heart rate	$>90/\text{min}$
Temperature	$<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$
Leukocytosis	<4000 or $>12000/\text{mm}^3$
Respiration	$>20/\text{min}$ or $\text{PCO}_2 <32 \text{ mmHg}$

Table 4. *Ranking of acute pancreatitis severity (12-15)*

Form	MODS/MSOF	Local complications	Systemic complications (comorbidities)
Medium	-	-	-
Moderately-severe	Transitory organ dysfunctions present (<48 hours)	And/or local complications present (sterile/infected)	And/or enhancement of some comorbidities
Severe	Persistent organ dysfunctions/failures present (>48 hours), One or more affected organs.	Local complications present (sterile/infected)	Enhancement of some comorbidities

and that its severity can change during its evolution (12-15,21). At admittance, the medium form of acute pancreatitis is identified through the absence of organ dysfunctions/failures. When the organ dysfunction is present during the first 24 hours (practically from the admittance on), it is difficult to establish the degree of severity, because we cannot know whether the organ dysfunction/failure is transitory or persistent (13). These patients must be initially classified and treated as potential carriers of the severe form of acute pancreatitis. If the organ dysfunction/failure relegates in the first 48 hours (transitory form), the patients will be considered to have a moderately-severe form of acute pancreatitis. Otherwise, the cases will continue to be considered a severe form (12). In the early stage, acute pancreatitis severity can be reevaluated daily, considering the disease's evolution nature. Usually, this reevaluation must take place at 24 and 48 hours and at 7 days from admittance (12,14). When local complications are identified in the early stage, reevaluation using imagery is not necessary because: 1) the presence and extent of pancreatic and peripancreatic necrosis cannot be defined clearly in the first week of development (16). At 5-6 days from admittance CECT is much more reliable in establishing the presence and extent of the necrosis; 2) the extent of necrosis and morphological changes aren't proportional to the degree of organ dysfunction/failure (15,16); 3) if in the first week the imagery identifies the presence of peripancreatic fluid collections or pancreatic/peripancreatic necrosis, surgical intervention is not yet necessary (6,7,45). In the late stage of the moderately-severe or severe form of acute pancreatitis, local complications evolve completely, even though some patients with persistent organ dysfunctions/failures can evolve favorably without local complications (40,41). On the other hand, the distinction between infected and sterile collections (already described) is highly important, both therapeutically and for prognostic. The presence of infection in necrotic areas is a certain growth marker for the mortality risk. Infected necroses without persistent organ dysfunctions/failures have a lower mortality rate than the forms in which they appear together (37). It is very important to differentiate the morphological features of local complications because each of these require certain interventions, depending on severity, for avoiding fatal therapeutic results (24,27,46).

Discussions and critical discussions

The new classification of acute pancreatitis based on the determining and sequential factors required a considerable effort, pursuing to establish with this step more precise definitions and classifications (10). Without claiming to create a therapeutic guide, we defined the acute pancreatitis diagnosis criteria, differentiated two forms of acute pancreatitis (interstitial/edematous and necrotic) and the fact that acute pancreatitis as a dynamic pathological process holds two progressive stages (early and late). These two stages are distinct from a physiopathological point of view (1,2). The first stage is characterized by the presence or absence of organ dysfunction(s) and very little by the local peripancreatic changes. Thus, we can say it is characterized by "functional" or "clinical" aspects that determine a certain therapeutic (conservatory) conduct (44). As opposed to the first, the second stage is characterized by the symptomatology determined by the evolution of local pancreatic/peripancreatic complications that can also manifest systemically, thorough bacteremia and sepsis. Thus, the "morphological" criteria hold the greater importance in the late stage, not overlapping with the early stage's criteria (44) and determining specific therapeutic sanctions.

One of the most important contributions of this revision is the redefinition of local complications, based on their content, the existence or absence of the wall, the occurrence site and the development in time (12-15). We consider that two aspects need to be emphasized. 1) "Pancreatic abscess" is not a term reflected in the new classification's terminology, because: depending on the stage of necrosis (solid, semi-solid, liquid) and the microorganisms involved in the sepsis, the quantity of collected pus varies greatly, so that in the late stages (encysted necrosis, WON) the collection can be made entirely of pus, with very little solid material (necrosis maturation process through liquefaction) (12,15). 2) The significance of the term "pancreatic pseudocyst" has been altered in both literature and medical dialogue, often being used to describe most peripancreatic exudate present in the development of acute pancreatitis (14). A particular pathological situation is the "disconnected duct syndrome", that can determine the forming of a pancreatic pseudocyst in patients with pancreatic necrosis (12,44). This phenomenon takes place a few weeks

Table 5. Definition and classification of the severity of acute pancreatitis in 4 degrees (4,9,10)

Degree of severity	Local complications		Systemic complications
Medium	No local complications	and	No MODS/MSOF
Moderate	Sterile local complications	or	Transitory MODS/MSOF
Severe	Septic local complications	or	Persistent MODS/MSOF
Critical	Septic local complications	and	Persistent MODS/MSOF

after necrosectomy, when the infected pancreatic necrosis of the neck or of the proximal body of the pancreatic parenchyma isolates a portion of distal viable parenchyma that continues to secrete through the interrupted duct in the remaining cavity post-necrosectomy. Another major contribution is the recognition of the dynamic character of the disease, its development having an implicit change in severity. Mortality and morbidity are determining factors in establishing a hierarchy in the degrees of severity (risk groups): patients with high morbidity and mortality (severe form), patients with high morbidity and low mortality (moderately-severe form), and patients with low morbidity and no mortality (medium form) (14). Although some workgroups suggested a 2-degree hierarchy of the severity (medium and severe, which, in our opinion, fail to reflect all the aspects of the physiopathological and clinical changes in the disease's development) or a 4-degree hierarchy (medium, moderate, severe and critical - in our opinion, more didactic, better suited for clinical research) (4,9,10), this last version, with 3 degrees of severity, defined especially by morbidity and mortality, agreed upon through majority consent, appears to be more easily mastered in medical practice, although we would like to bring a few critiques. First of all, the rationale upon which all local complications, sterile or infected, were included in the moderately-severe form is not very clear, this aspect also being pointed out by Petrov (10). As we know, the infection of the pancreatic necrosis indicates a completely different degree of severity than the simple presence of an acute sterile peripancreatic collection of fluid. Secondly, an ideal classification should reflect the whole area of clinical and paraclinical changes for one patient, at a given time. In the chosen classification, the main variable that characterizes the degree of severity is only the transitory or persistent organ dysfunction(s)/failure(s), without taking into account, gradually (absent, sterile, infected), the relevant changes of the local complications that can influence the general status of any patient suffering from acute pancreatitis (47). These clinically significant variables, also important for prognostic and use in research, stood as the basis of the suggested hierarchy of severity, distinguishing 4 categories (Table 5) (4,9,10). Thirdly - the inclusion of systemic complications (exacerbation of the existing comorbidities), in the moderately-severe form, which, in our opinion, are more of a consequence of rather than a cause for acute pancreatitis (14).

Conclusion

In the end, we can agree that the number of degrees of severity has less significance than the basis of classification (14). From the clinician's point of view, persistent dysfunction(s)/

failure(s) are predictive for death (37). Local complications without an organ dysfunction are associated with high morbidity rates, prolonged hospitalization, but decreased mortality. Hence, setting the hierarchy for the severity of acute pancreatitis remains the key element in the approach of this pathology (9, 10). As is the case for every new classification system, in order to prove its efficacy the system will have to be implemented in current practice and then closely evaluated, from both a medical practice perspective and through clinical studies. We think that the accurate description of local complications and of the natural evolution of the disease's specific stages, along with the standardization of terminology will improve the therapeutic management and scientific research data reporting quality.

Conflict of interest

The authors have no conflict of interest.

Authors contribution

D. Cochior has accepted the invitation of the Professor of Surgery E.P. Dellinger (Washington University, Seattle, USA) to participate in this international survey (2012), analyzed all our medical cases (1994-2013), conceived and drafted the present manuscript, contributed to the iconography selection and performed the surgery in the Department of Surgery of the Clinical Hospital CF 2 Bucharest, corresponding author; S. Constantinoiu analyzed all our medical cases, partial drafted the present manuscript, contributed to the iconography selection and performed the surgery in the Department of General and Esophageal Surgery „St. Mary” Hospital, Bucharest; C. Copăescu contributed to the selection of the iconography, drafted and highlighted aspects of the best laparoscopic surgical approach; D. Șerbănoiu analyzed the iconography with lead author and is a member of the operating team; Rodica Birlă, analyzed the iconography with lead author and is a member of the operating team; M. Boeriu made English translation of the article and is a member of the operating team. The new classification of acute pancreatitis was communicated to the authors by oral presentation at the National Conference of Surgery - Sinaia 2013

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