

Clinical assessment and management of severe acute pancreatitis: a multi-disciplinary approach in the XXI century

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Abstract: Acute pancreatitis (AP) is the most common gastrointestinal disorder requiring hospitalization, with a high rate of morbidity and mortality. Severe AP is characterized by the presence of persistent organ failure involving single or multiple organs. Clinical evolution, laboratory and radiological assessment are necessary to evaluate the prognosis and inform the management of AP. The onset of severe AP may be classified in two principal phases. The early phase, during the first week, is characterized by the activation of the auto-inflammatory cascade, gut dysbiosis, bacterial translocation, and the down-regulation of immune responses. The late phase is characterized by the development of local and systemic complications. Several old paradigms have been amended in the management of AP patients, such as the indication of nutrition, the use of antibiotic therapy, pain control strategies, and even the use of surgery. Real world evidence has shown that in the majority of cases a step-up approach is most effective. In this review, we discuss the clinical assessment and improvements to the management of patients with severe AP in a high volume center where a multi-disciplinary approach is performed.

Key Words

Acute pancreatitis, Fluid resuscitation, Enteral nutrition, Antibiotic therapy, Pain management, Step-up approach.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas¹. It is the most common gastrointestinal disorder requiring hos-

pitalization, with a significant impact in morbidity and mortality². It has a worldwide incidence of 13–45 cases per 100,000 persons³. AP may develop in two principal forms, interstitial edematous pancreatitis with a mortality of less than 3%, and necrotic pancreatitis with a mortality of higher than 15%³. The rate of hospitalization for AP continues to increase as a consequence of the persistence of several risk factors⁴, such as chronic alcohol use or abuse, that diffusely are present in the global population. Recently, the 1992 Atlanta criteria have been revised and a new classification for AP has been proposed⁵. This last current global consensus classification of AP offers a comprehensive arrangement of clinical severity and diagnostic and therapeutic management. The new proposed classification precisely evaluates early and late AP related complications with a special emphasis on peripancreatic fluid collections, that have been divided into four principal subtypes. Due to its complexity, AP management requires the intervention of several specialists, such as the internist/gastroenterologist, endoscopist, radiologist, and surgeon, who may cooperate in a multidisciplinary approach. The early phase of mild AP is often successfully treated with conservative measures, mainly with aggressive fluid rehydration, to ensure the maintenance of survival functions. Severe AP, on the other hand, often requires admission to the intensive care unit (ICU), while the late phase of severe pancreatitis may require percutaneous and endoscopic techniques and even surgery, in the light of the step-up approach, to deal with the complications of the disease process⁶.

Etiology and risk factors

The principal causes of AP are choledocholithiasis (about 40% of cases) and chronic alcohol use or abuse (about 30% of cases). Other causes include iatrogenic pancreatitis, such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound-fine needle aspiration/biopsy (EUS-FNA/FNB, about 10% of cases), drugs⁷, such as steroids, NSAID, azathioprine, mercaptopurine, mycophenolic acid, fenofibrate, estrogens, mesalazine, infliximab, angiotensin-converting enzyme inhibitors, furosemide, thiazide diuretics, statins, several antibiotics, valproic acid, olanzapine, etc. (about 5% of cases), autoimmunity (< 5% of cases), obstructions (< 5% of cases)⁸, hypertriglyceridemia (< 5% of cases), and hypercalcemia (related to excessive vitamin D therapy, hyperparathyroidism, total parenteral nutrition). Finally, rare causes of AP are infections, toxins, traumatic events, genetic causes (mutations in CFTR/PRSSI/SPINK1 gene), and vascular anomalies (ischemia, vasculitis)^{6,9} (Table I).

The diagnosis of acute pancreatitis and the assessment of clinical severity

According to the 2012 Atlanta criteria⁵, the diagnosis of AP requires two of the following three features:

- (1) Abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back);
- (2) Serum lipase or amylase at least three times greater than the upper limit of normal;
- (3) Typical radiologic findings of acute pancreatic damage on transabdominal ultrasonography (US) contrast-enhanced computed tomography (CECT), and, less commonly, magnetic resonance imaging (MRI) (Table II).

However, if the diagnosis of AP can be performed only with clinical symptoms and laboratory *criteria*, the standard guidelines recommend that computed tomography (CT) should not be performed at admission to determine the severity

Table I. Causes, frequency and risk factors of acute pancreatitis.

Causes of acute pancreatitis	Frequency
Gallstones	40%
Alcohol	30%
Iatrogenic: ERCP, EUS-FNA/FNB, abdominal surgery	10%
<i>Drugs</i> Such as: steroids, NSAID, azathioprine, mercaptopurine, mycophenolic acid, fenofibrate, estrogens, mesalazine, infliximab, angiotensin-converting enzyme inhibitors, furosemide, thiazide diuretics, statins, several antibiotics, valproic acid, olanzapine, etc.	5%
Autoimmunity (IgG4 related disease)	< 5%
<i>Obstruction</i> Such as: congenital pancreatic variants and anomalies, malignant pancreatic duct or ampullary obstruction, pancreatic macrocysts (pseudocysts, IPMN, cystadenomas), etc.	< 5%
Hypertriglyceridemia, hypercalcemia	< 5%
Infections (viruses, parasites, etc.)	< 1%
Traumatic events	< 1%
Vascular anomalies (ischemia, vasculitis)	rare
<i>Genetic causes</i> Such as: cystic fibrosis, mutations in CFTR/PRSSI/SPINK1 gene, deficiency of lipoprotein lipase, etc.	rare
Risk Factors	
Smoking, obesity, metabolic syndrome and diabetes	common
Pancreas divisum, sphincter of Oddi dysfunction	controversial
Celiac disease, IBD, surgical procedure like cardiopulmonary bypass	uncommon

List of Abbreviations: ERCP: endoscopic retrograde cholangiopancreatography; EUS-FNA/FNB: endoscopic ultrasound-fine needle aspiration/fine needle biopsy; NSAID: non-steroid anti-inflammatory drugs; IPMN: intraductal papillary mucinous neoplasm; CFTR: cystic fibrosis trans-membrane conductance regulator; PRSSI: polymorphisms in cationic trypsinogen; SPINK1: polymorphisms in serine protease inhibitor kazal type 1; IBD: inflammatory bowel diseases.

Table II. The revised Atlanta criteria for the diagnosis of acute pancreatitis.

<p>The diagnosis of acute pancreatitis requires two of the following three features:</p> <ol style="list-style-type: none"> 1 Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); 2 Serum lipase or amylase at least <i>three times</i> greater than the upper limit of normal; 3 Typical radiologic findings of acute pancreatic damage on contrast-enhanced computed tomography (CECT) and/or on magnetic resonance imaging (MRI) or transabdominal ultrasonography.

of disease, but it may be performed after 5-6 days from the onset of symptoms to assess the presence of AP complications^{10,11}. On the contrary, CT is necessary in the initial patient evaluation if the typical pancreatic abdominal pain is not associated with an increase in amylase or lipase level^{4,5,12}. Several classifications of AP have been proposed¹³. The current global consensus *criteria* propose a new classification of AP into three categories of severity, and classify peripancreatic collections into four groups in relation to their morphology and imaging findings⁵. Thus, according to the last revision of the 2012 Atlanta *criteria*, the severity of AP may be stratified in relation to the presence of transient or persistent organ failure and the presence or absence of local and systemic complications (Table III). Consistent with this terminology, transient organ failure is defined as an organ failure that is present for <48 h; conversely, persistent organ failure lasts more than 48 h. Local complications include peripancreatic fluid collections, characterized according to the presence of only fluid contents or acute ne-

Table III. Causes, frequency and risk factors of acute pancreatitis.

Severity	Criteria
Mild	No organ failure No local complications No systemic complications Typically resolves in first week.
Moderate	<i>Transient organ failure</i> (≤48 h) <i>or</i> <i>Local complications:</i> fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis (WON). <i>or</i> <i>Systemic complications:</i> exacerbation of pre existing co-morbidity (such as coronary artery disease, chronic lung or kidney disease) without persistent organ failure.
Severe	<i>Persistent organ failure</i> (>48 h) - Single organ failure; - Multiple organ failure (MOF).

crotic debris and divided into four principal types. Hence, the new proposed classification divides AP into three severity groups: mild, moderately severe, and severe pancreatitis (Table IV).

Mild acute pancreatitis is characterized by the absence of organ failure, both transient and persistent, and the absence of any complications. Patients with mild AP may need only clinical observation and may be discharged quite quickly during the early phase. If the diagnosis of pancreatitis is sufficiently clear, patients should not require pancreatic imaging. The severity of mild pancreatitis is low and mortality is very rare.

Table IV. The 2012 revised Atlanta Classification Criteria⁵: definitions and terminology.

Feature	Signs and symptoms
Organ failure	<ul style="list-style-type: none"> - Shock: systolic blood pressure <90 mmHg; - Pulmonary failure: PaO₂ <60 mmHg; - Renal failure: serum creatinine >2 mg/dL (after rehydration therapy); - Gastrointestinal bleeding: >500 mL/24 h.
Local complications	<ul style="list-style-type: none"> - Acute peripancreatic fluid collection: complications acute fluid collection without a well defined wall, confined by normal fascial planes, <4 weeks; - Pancreatic pseudocyst: collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, >4 weeks; - Pancreatic necrosis (>30% of the parenchyma or >3 cm): <ul style="list-style-type: none"> o Acute necrotic collection: collection containing variable amount of fluid and necrotic tissue, <4 weeks; o Walled-off necrosis (WON): mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well defined inflammatory wall, >4 weeks; - Pancreatic abscess (infected necrosis): circumscribed collection of pus containing little or no pancreatic necrosis.

Moderately severe acute pancreatitis is characterized by the presence of transient organ failure, (lasting less than 48 hours) affecting one or more organs. Local or systemic complications may also occur.

Severe acute pancreatitis is characterized by the presence of persistent organ failure (>48 h). Organ failure may involve single or multiple organs, (multi-organ failure (MOF)). Organ failure in the early phase of AP is due to the activation of the pro-inflammatory cytokine cascade, leading to the systemic inflammatory response syndrome (SIRS). Patients that develop persistent organ failure within the first few days of the disease usually have also one or more complications. Severe AP is associated with an elevated risk of death with a reported mortality rate of 36-50%^{5,14,15}. Finally, the development of infected necrosis among patients with persistent organ failure is associated with an extremely high mortality¹⁶.

Laboratory Tests

AP is typically an inflammatory process of the pancreas, characterized by the activation of local cellular autolytic mechanisms due to excess pancreatic enzyme production and activation. The consequence of this inflammatory process is transient pancreatic parenchymal damage. According to this pathogenetic progression, the increase in pancreatic serum enzymes contributes to the diagnosis of AP. In fact, in the early phase of AP, there is a breakdown of the physiological synthesis-secretion coupling of pancreatic enzymes. In particular, pancreatic enzyme synthesis continues while secretion is blocked. As a consequence, the enzymes leak out of acinar cells through the basolateral cellular membrane, and then enter into the systemic circulation¹⁰. Thus, the increase in serum amylase and lipase level is linked to an acute pancreatic inflammatory process, and assessing the serum levels of these can assist in diagnosis, classify the severity of disease, and even predict outcomes⁶.

According to the global consensus *criteria*, an increase in lipase or amylase level greater than three times the normal amount is considered diagnostic for AP¹⁷. Lipase level testing is more sensitive and specific than amylase level testing, because amylase is also produced by the salivary glands. Moreover, other extra-pancreatic conditions may be associated with an increase in amylase level, such as alcohol abuse, several inflammatory intestinal diseases, abdominal traumas, malignancies with ectopic amylase production,

fallopian tube diseases, renal failure, macroamylasemia, and others¹⁸. It is important to remember that serum amylase levels may be normal in alcohol-induced AP, due to the inability of the alcohol-damaged parenchyma to produce amylase, and in hypertriglyceridemia-associated pancreatitis, as triglycerides interfere with the amylase assay¹¹. In addition, a lipase/amylase *ratio* greater than 4 or 5 strongly supports an alcoholic cause of pancreatitis^{19,20}. Serum amylase levels typically rise within 6-12 hours of the onset of AP. Amylase has a short half-life of approximately 10 hours and in mild pancreatitis generally returns to normal within 3-5 days. In consideration of the short half-life of amylase, the diagnosis of AP may be missed in patients who present >24 h after the onset of symptoms²⁰. Thus, serum lipase levels are a more sensitive and specific indicator of AP than serum amylase levels. Serum lipase levels rise within 4-8 hours of the onset of symptoms, peak at 24 h, and return to normal within 8-14 days¹⁸. Thus, lipase level elevations occur earlier and last longer as compared with elevations in amylase, making lipase testing more reliable in patients who present >24 hours after the onset of pain¹¹.

Other tests may be performed in the initial assessment of patients with suspected AP, such as complete blood count, comprehensive metabolic panel including renal and hepatic function, and measurement of calcium, lactate dehydrogenase (LDH), and triglyceride level. Depending on the clinical setting, further measurement of arterial blood gas may be useful.

These laboratory tests which evaluate the clinical symptoms and assess vital functions may allow the calculation of several scores that can be used to predict clinical severity, morbidity, mortality, and outcome of AP²¹. The most utilized scores are Ranson's *criteria*, APACHE-II (Acute Physiology and chronic Health Evaluation) score, and BISAP (Bedside Index for Severity in Acute Pancreatitis) score²². Of these, the BISAP score represents a simple way to identify patients at risk of increased mortality and the development of intermediate markers of severity within 24 hours of presentation. The BISAP score provides a single point for each of five parameters: age > 60 years, blood urea nitrogen (BUN) > 25 mg/dL, the presence of a pleural effusion, impaired mental status, and/or systemic inflammatory response syndrome (SIRS), for a possible total of five points. A BISAP score greater than three is associated with a 7-12 fold increase in the risk of developing organ failure²³. Furthermore, clinical evidence has demonstrated that an

APACHE-II score equal to or greater than eight points has been confirmed as an optimal score for predicting a more severe course of AP^{24,25}. Finally, an increase in serum levels of aminotransferases and/or bilirubin, gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) at the onset of symptoms may suggest a biliary etiology of AP. However, an increase in these serologic markers may be also related to the inflammation and the pancreatic edema typically associated with the early phase of AP. For this reason, in the case of increased biliohepatic blood tests, it is helpful to perform an abdominal ultrasound and/or CT assessment to rule out the possible presence of pancreatic-biliary stones or obstructions. In conclusion, the initial management of AP aims to define the clinical severity of the disease, and then to assess and treat the fluid losses and the organ failure (particularly renal, cardiovascular and respiratory impairment). Thus, the assessment of the vital parameters, and the organ function blood tests are essential in the management of early phase of AP patients.

Radiologic Evaluation

At the onset of symptoms, all patients should undergo abdominal US. CECT is indicated when the clinical assessment is not adequately clear and in case of increased hepato-biliary blood tests. At the onset of symptoms, it is essential to rule out the possible presence of biliary causes of AP, such as stenosis or gallstones in the gallbladder or the bile duct, which may quickly require specialist treatment. However, in the early phase of AP, the presence of bowel gas due to the paralytic ileus associated with pancreatic inflammation may obscure transabdominal US evaluation of the pancreas and bile duct system. The literature data reported that only in 25-45% AP patients the abdominal US is able to study the pancreatic and peripancreatic region²⁶. The abdominal US is not adequate to clearly define the extrapancreatic spread of pancreatic inflammation or identify necrosis within the pancreas. Finally, abdominal US may be useful in the evaluation of late local AP complications, such as peripancreatic fluid collections, that may appear anechoic or corpusculated and may present internal echoes. The presence of corpusculated fluid collection at abdominal US may indicate pancreatic necrosis and thus require further radiological evaluation with CECT or MRI. Multidetector CT (MDCT) is the most suitable technique due to its availability, easy access, and diagnostic accuracy. Scan protocols using a 64 or higher rows CT scanner

are based on a plan study, followed by contrast enhanced arterial parenchymal phase (pancreatic phase) and portal venous phase²⁷. Both phases have a complementary role for evaluation of edema, pancreatic and peripancreatic fluid collections and necrosis. MDCT scan is not recommended in the early phase of AP because there is no evidence that CT improves clinical outcomes. CT scan may be delayed at least 72 h after the onset of symptoms when local acute complications such as pancreatic and peripancreatic fluid collections and necrosis, may appear¹². If clinical symptoms persist (abdominal pain, fever, nausea), CECT can detect acute interstitial edematous pancreatitis including focal or diffuse enlargement of the pancreas with heterogeneous enhancement (Figures 1-4). CECT has prognostic value, facilitating the use of a severity score (the Balthazar score) that takes into consideration the presence of inflammation, fluid collections, and necrosis. In its initial evaluation, the Balthazar score suggested that AP may have up to 25% mortality in the presence of pancreatic necrosis. This score showed a linear association between necrosis >30% and morbidity and mortality²⁸. Finally, CECT is useful to visualize gallbladder or common bile duct stones, and other causes of biliopancreatic ductal stenosis, such as papillary, duodenal and pancreatic masses, obstruction or dilatation of the Wirsung duct, and cystic pancreatic lesions, such as serous and mucinous cystadenoma, and intraductal papillary mucinous neoplasia (IPMN)²⁹. Magnetic Resonance Imaging (MRI) with T2-weighted (T2w), DWIw, T1w and contrast enhanced dynamic sequences, may be considered comparable to CECT in the early assessment of AP patients (Figure 5)²⁷. MRI has a higher sensitivity for the diagnosis of choledocholithiasis down to 3 mm diameter and pancreatic duct disruption as compared with CECT³⁰. Magnetic resonance cholangiopancreatogram (MRCP) is comparable to endoscopic retrograde cholangiopancreatogram (ERCP) for the detection of choledocholithiasis³¹. Furthermore, MRI has the advantage of avoiding X-ray, and also gadolinium has a lower risk of nephrotoxicity as compared with the iodinated contrast of CECT. Thus, MRI may be performed when pancreatic duct disconnection is suspected, although a normal MRCP may be insufficient for the exclusion of a disconnected duct in the presence of suspicious features. Moreover, MRI can be used to differentiate exudative fluid collection from those that have solid components from the necrosis process, before drainage of fluid collections²⁷.

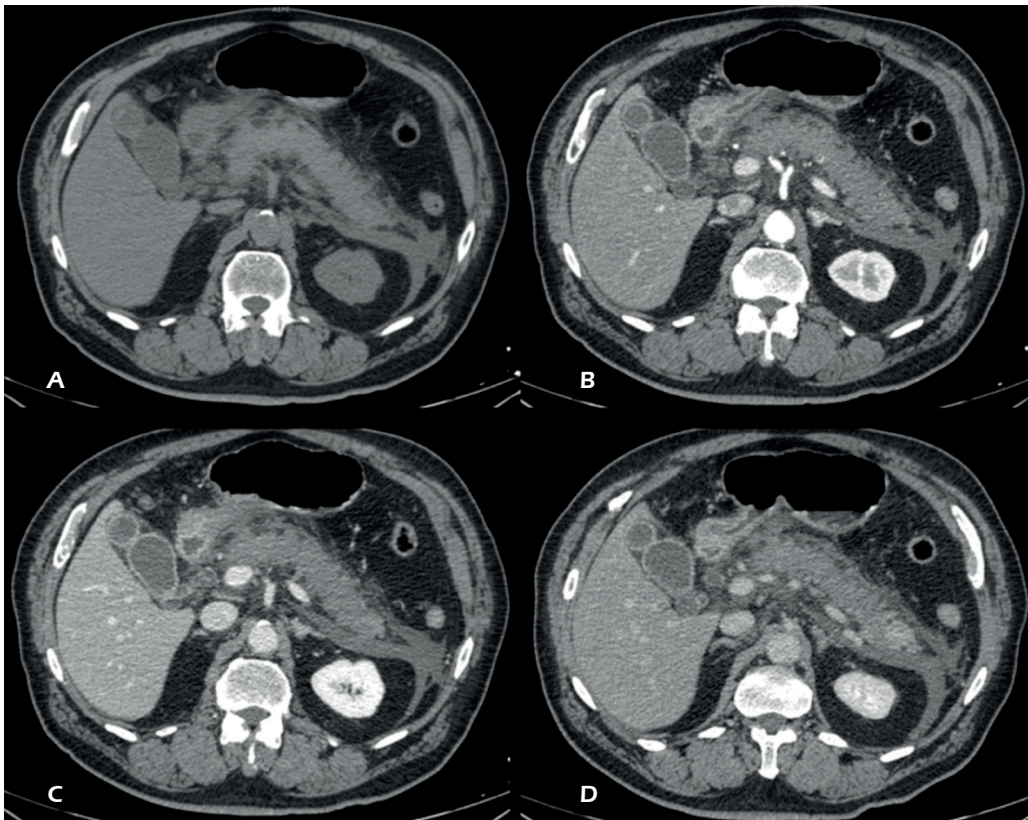


Figure 1. CT of 76-year-old man with acute onset of pancreatitis. Unenhanced (A) and post-contrast (B-D) CT scan show acute fluid collection without perceptible wall that is conforming to its surrounding structures anterior the tail of pancreas and left-anterior pararenal space. Enhanced dynamic CT images show reduced enhancing parenchyma, but no evidence of necrosis.

Clinical evolution

The revised Atlanta classification has divided the severity of AP into mild, moderately severe and severe. Mild AP usually has a subclinical

course, may occur with few symptoms and no organ dysfunction, and often improves spontaneously and heals within a few days. Conversely, moderately severe and severe AP are usually necrotizing pancreatitis and may be associated with

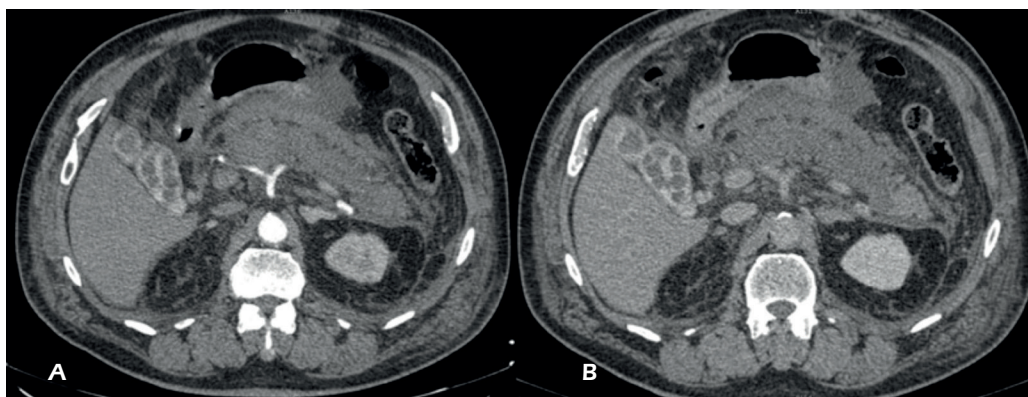


Figure 2. Enhanced CT scan (pancreatic phase in A and portal phase in B) 2 days post onset of acute pancreatitis symptoms shows increased peripancreatic fluid collection and parenchyma necrosis; multiple negative gallbladder stones are shown by hyperdensity bile.



Figure 3. Enhanced CT scan 20 days post onset of acute pancreatitis symptoms shows large heterogeneous fluid collection in lesser sac that displaces stomach anteriorly.

life-threatening local and systemic complications. AP should not be considered a static disease because its clinical course is characterized by a rapidly evolving dynamic status⁵. Hence, the clinical evolution of moderate and severe AP generally may be classified in two principal phases. The early phase occurs in the first week, and is characterized by the development of a complex systemic inflammation that may even proceed to multi-organ failure (MOF). The complete pathophysiology of the AP-induced MOF has not fully understood³². It is known that the early phase of

AP is characterized by the pathological activation of pancreatic enzymes within the pancreatic gland leading to the autodigestion of pancreatic tissue. This autodigestion of the pancreatic gland leads to the activation of local and systemic inflammation³³ with the hyper-production of several pro-inflammatory cytokines³⁴ and acute phase proteins, such as TNF-alpha³⁵, IL-6, and C-Reactive Protein (CRP)³⁶. At this point, two other mechanisms may worsen this intricate inflammatory cascade: overgrowth of gut bacteria and the related bacterial systemic translocation, followed by the down-regulation of the immune system^{37,38}. Thus, the breakdown of the physiological interplay between gut microbiota and the immune system in the gut determines the activation of systemic inflammation and even is able to predispose to the systemic infections that typically occur in the late phase of AP. Hence, the early phase of AP is profoundly characterized by the activation of local and systemic inflammatory cascade, bacterial overgrowth and bacterial translocation, and the down-regulation of the immune system. All these favour late phase infectious complications, persistent organ failure, and even death. These mechanisms explain why infections usually occur only after the first 7 days from the onset of AP. The late phase of severe AP is characterized by the development of local and systemic complications due to the activation

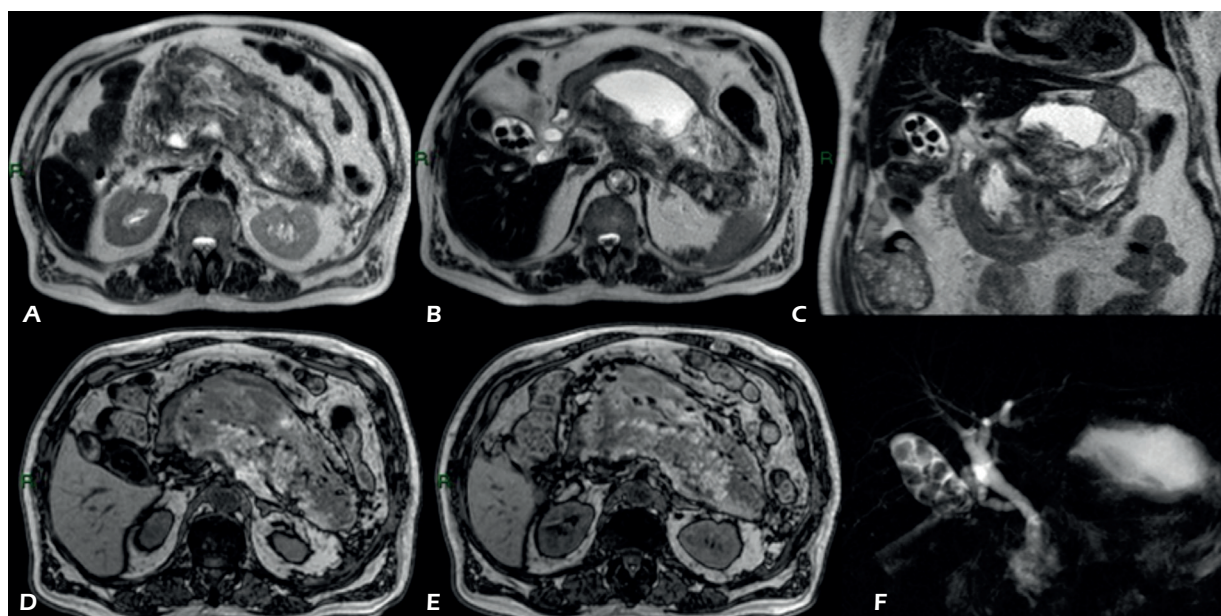


Figure 4. MR imaging acquired 6 weeks post onset of acute pancreatitis symptoms reveals evolution of heterogeneous combined pancreatic-peripancreatic collection into well-defined wall-off necrosis (WON). Hyperintense fluid and hypointense non-liquefied components are shown in T2w sequences (A-C), as well as multiple gallstones; T1w out of phase sequence (D, E) confirms hyperintense debris into the collection. MR cholangiopancreatography (MRCP) (F) shows gallbladder and biliary duct lithiasis.

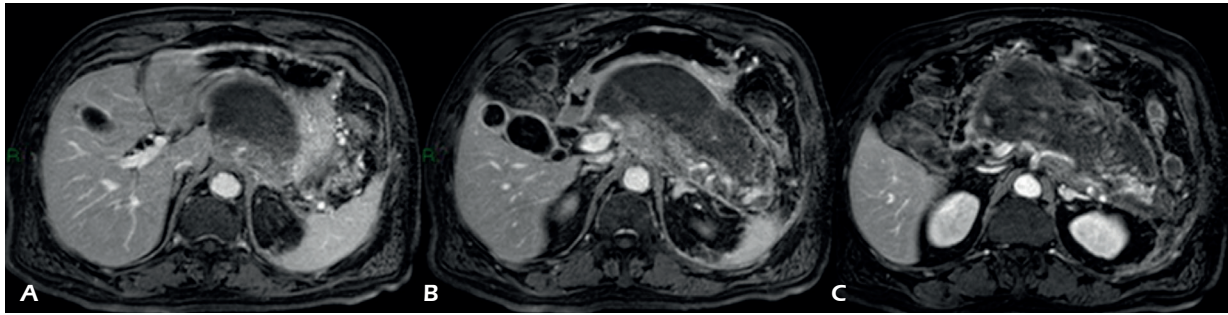


Figure 5. MR imaging acquired 6 weeks post onset of acute pancreatitis symptoms. Axial contrast-enhanced fat-saturated T1w sequence obtained in venous phase reveals ill-defined hypoattenuating areas in the head, body and part of tail of the pancreas and a well-defined, heterogeneous peri-pancreatic necrotic collection (WON).

of the inflammatory cascade and the down-regulation of the immune response. Late complications occur in about 1/3 of severe AP patients. Local complications include peripancreatic fluid collections, necrotic collections, pancreatic pseudocysts and walled-off necrosis (WON). A potential local complication of severe AP is the development of pancreatic necrosis infection, a condition requiring antibiotic treatment and percutaneous and/or endoscopic debridement, and in the more severe cases, even surgical intervention. Other local complications are biliary duct obstructions, gastrointestinal perforation or intestinal occlusion as a result of retroperitoneal inflammation, splenic infarction and thrombosis or pseudoaneurysms with hemorrhagic risk, and also pancreatic ascites^{39,40}. Systemic severe AP complications involve the development of systemic infections, multi-organ dysfunction syndrome (MODS)⁴¹ and even death. In this way, it is notably important to distinguish sepsis from SIRS, although their clinical presentation may be analogous. Sepsis is a secondary condition requiring antibiotic treatment, while the use of antibiotics is not necessary and would be avoided in SIRS⁴². In conclusion, severe AP develops in distinct phases. The early phase is characterized by systemic inflammation due to bacterial overgrowth and translocation until MODS, and the late phase is characterized by the development of local and systemic inflammation. These two phases are related to the two peaks of morbidity and mortality associated with severe AP (Figure 6).

Management

The management and therapy of AP may be focused according to the severity of the disease. Mild AP is usually a self-limiting disease that

spontaneously improves until completely healed⁶. Thus, this condition does not require specific therapies. On the other hand, moderate and severe AP may be life-threatening, requiring Intensive Care Unit (ICU) hospitalization, and may be lethal. As discussed above in this manuscript, the early phase of severe AP is characterized by the shift from local to systemic inflammation. During this phase, happening in the first several hours, numerous pathophysiological events occur, such as a profound fluid redistribution due to a substantial third-space loss (in the retroperitoneal space, intestine, etc.), and intravascular volume depletion⁹. These events have a negative impact on systemic circulation leading to blood hemoconcentration and several organ failures, such as acute renal impairment and alterations in the base-acid equilibrium and serum electrolytes (particularly hypocalcaemia due to the precipitation of this ion in the peri-pancreatic fluid collections). In the last decades, various pharmacological agents have been tested in the treatment of the early phase of severe AP, such as somatostatin or octreotide that decrease pancreatic secretions; protease inhibitors, such as gabexate mesylate, aprotinin, and ulinastatin; antioxidants such as vitamin C and n-acetylcysteine. However, all the clinical trials utilizing these agents have not demonstrated a real benefit in their use in AP^{43,44}. In particular, the data on octreotide is quite controversial. Andriulli et al⁴⁵ shown that octreotide in AP patients may reduce mortality but not complications. On the other hand, Xu et al⁴⁶ shown that octreotide does not appear to be beneficial in major clinical outcomes related to moderate and severe AP. In this way, a recent Cochrane meta-analysis agreed with Xu et al⁴⁵ and disagreed with Andriulli et al⁴⁵ considering the poor efficacy of octreotide in treating moderate and severe AP.

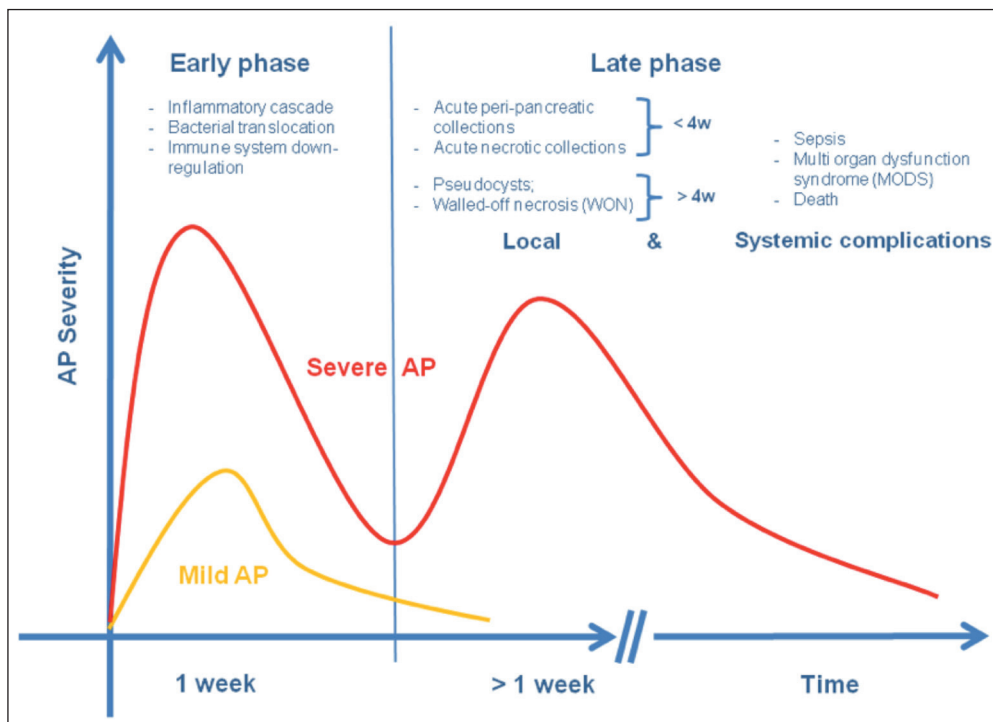


Figure 6. The two phases of acute pancreatitis (severe AP). Severe AP develops in two distinct phases. The early phase is characterized by systemic inflammation due to bacterial overgrowth, bacterial translocation, and the down-regulation of the immune system. These mechanisms explain why infections usually occur only after the first 7 days from the onset of AP. Then, the late phase of severe AP is characterized by the development of local and systemic complications that occur in about 1/3 of severe AP patients. Local complications include peripancreatic fluid collections, necrotic collections, pancreatic pseudocysts and walled-off necrosis (WON). Systemic complications involve the development of systemic infections, multi-organ dysfunction syndrome (MODS), and even death. These two phases are related to the two peaks of morbidity and mortality associated with severe AP. (Abbreviations: AP, acute pancreatitis).

Fluid Resuscitation

The acute phase of severe AP is characterized by a profound fluid redistribution causing hypovolemia and blood hemoconcentration and consequent worsening of renal function, alteration in the base-acid equilibrium, and blood electrolytes. For these reasons, the management of the early phase of AP aims principally to resolve these alterations in the fluid balance⁴⁷. Several studies have confirmed that timely, intense fluid resuscitation in the first 24 hours after the onset of symptoms may be able to reduce the morbidity and mortality of AP^{6,32,48}, in spite of evidence that rapid hemodilution can increase the incidence of sepsis⁴⁹. Fasting fluid resuscitation during the first 24 hours is able to restore fluid depletion and preserve systemic circulation and kidney function. Recent guidelines suggest administering about 2.5-4 L of crystalloid solutions (such as Ringer's lactate and normal saline) during the first 24 hours, corresponding to the dosage of 2 ml/kg/h, with an initial bolus of 20

ml/kg in the first hour^{9,48}. In severe AP patients, the total volume of fluid resuscitation may be up to 12 L in the first day. Ringer's lactate has been demonstrated to be superior to normal saline in the reduction of the inflammatory response⁵⁰. Colloids solution may also be used, following the recommended crystalloid/colloid ratio of 3/1⁴⁸. Furthermore, in the early phase of AP a continuous multi-parametric assay is necessary to carry out the clinical evolution of the patients. Effective fluid resuscitation therapy may be able to restore normal heart and respiratory rate, blood pressure, and urinary output⁵¹. In particular, the response to fluid resuscitation may be considered effective if urine output is restored at above 0.5 mL/kg/h⁴⁴. Finally, a daily blood test assay in severe AP patients is useful to evaluate blood fluid balance, renal function, and electrolytes. A reduction in serum calcium concentration of about 30% or < 8 mg/dL predicts a poor outcome. In this way, serum calcium value is utilized in the Ranson score at 48 h from the onset of symptoms⁵².

The Role of Nutrition in Acute Pancreatitis

Feeding in severe AP patients has always been a debated issue. According to an old paradigm, AP patients would have been fasted as long as possible, because food was considered an enemy of the inflamed pancreas. Then, it was thought to administer parenteral nutrition in all the severe AP patients. However, several clinical trials comparing parenteral to enteral nutrition have demonstrated that parenteral nutrition is associated with worse clinical outcomes and higher infectious risk⁵³. The prolonged enteral starvation is linked to gut nutrient deprivation, atrophy in the gut-associated lymphoid tissue (GALT), loss of the physiological enterocytes adhesion, overgrowth of pathological bacterial species, and induction of an endoluminal pro-inflammatory pattern with an over-expression of NF- κ B related cytokines and several mediators of inflammation⁵³. All these mechanisms are connected to a breakdown in the integrity of the gut mucosal barrier, causing a condition known as 'leaky gut' that in turn is responsible for the systemic translocation of bacteria and the various associated mediators of inflammation, such as the Gram-negative related lipopolysaccharide (LPS). Moreover, the inflammatory cascade may worsen pancreatic inflammation, and the related systemic translocation of pancreatic enzymes is a further mechanism contributing to the development of MODS. Indeed, prolonged enteral starvation is linked to an increase in systemic infections, sepsis, organ failure, and even death. Another debated point in the management of patients during the early phase of severe AP is the best choice of enteral feeding modality. In the past, it was thought that nasojejunal tube would have ensured only minimal stimulation of the pancreatic function. However, several randomized clinical trials (RCT) comparing enteral feeding with nasogastric vs nasojejunal tube have demonstrated that there are no significant differences in mortality rate, length of hospital stay, and infectious complications comparing both these feeding modalities⁵⁴. Thus, nasogastric feeding may be the most feasible choice in clinical practice, since nasogastric tubes are easy to place, well tolerated, and effective in ensuring an appropriate nutrition of AP patients. Another consideration in the management of the early phase of severe AP patients is the timing of enteral nutrition. Recent clinical acquisitions have shifted the old paradigm of maintaining AP patients at rest for long periods. In fact, several

meta-analyses have demonstrated the advantages of enteral feeding within the first 48 hours of the onset of AP symptoms^{55,56}. A clinical study⁵⁷ would seem to have even demonstrated that very early nutrition started within the first 24 hours may be associated with a minor rate of complications. According to the evidence, the latest AP guidelines of the Italian Society for the Study of Pancreas Pancreatic (AISP) recommend starting enteral feeding within the first 24-48 hours from the onset of symptoms⁴⁸. Accordingly, the latest AP guidelines of the American Gastroenterological Association (AGA) and of the International Association of Pancreas (IAP) recommend^{11,12}:

In the case of mild AP: early re-feeding, when nausea, vomiting, and abdominal pain are resolved, and after amylase and lipase reduction;

In the case of predicted severe AP (APACHE >7 at 48 h, CRP > 150 mg/L, in the presence of SIRS at 48-72 h): start with naso-enteric tube feeding.

Finally, two recent RCTs have shown that in the case of severe AP very early tube feeding before 48 h is not better than delayed on-demand oral feeding at 72 h in the reduction of death and infectious complications rate^{58,59}.

In conclusion, the pancreatology field has recently been altered by several clinical acquisitions and discoveries that have completely changed the clinical approach and management of AP patients. At the end of 90's it was proven that enteral nutrition is superior to parenteral nutrition. Additionally, the old paradigm of the benefits of prolonged starvation of the inflamed pancreas has been completely reversed, and in the last ten years, it has been demonstrated that early enteral feeding is better than prolonged enteral rest. The last step in this knowledge chain has been that the very early feeding of severe AP patients with an enteral tube is not superior to an on-demand oral diet. Thus, more than 20 years of clinical studies permitted us to conclude that feeding of AP patients with physiological modalities remains the better choice for these patients.

The Role of Antibiotic Therapy in Acute Pancreatitis

The early phase of AP is characterized by the systemic activation of the inflammatory cascade that may involve several organs and systems associated with SIRS. AP related- SIRS is connected to pulmonary atelectasis and pleural effusion and consequently to acute respiratory insufficiency, fluid redistribution and electrolytes disorders contributing to acute pre-renal impair-

ment, hemodynamic alterations, and alterations in body temperature. Other complications may occur, such as gastrointestinal bleedings and pancreatic and peri-pancreatic haemorrhages leading to anaemia, sepsis and septic shock^{60,61}. Because of this, it is extremely important to distinguish between SIRS and sepsis, because although the clinical presentation may be very similar, the therapy is completely different. While using antibiotic therapy is unnecessary and even harmful in the case of SIRS, it is absolutely needed in the case of extra-pancreatic infections, such as cholangitis, pneumonia, urinary tract infections, or in the case of sepsis, and septic shock. These infectious complications should receive appropriate antibiotic therapy⁴⁸. It is also very important to distinguish between sterile vs. infected necrosis that may have a similar clinical presentation yet be profoundly different in prognosis and treatment⁶².

In the past 40 years, several RCTs and meta-analyses have been performed to assess the efficacy of the prophylactic use of antibiotic therapy in preventing infectious complications in severe AP patients^{43,44,63-66}. Overall, these literature data have shown contrasting results definitely not supporting the routine use of prophylactic antibiotic therapy to reduce the occurrence of AP-related infectious complications, such as necrosis infection and sepsis, use of surgery, and even mortality⁶⁷⁻⁶⁹. Therefore, to date, international guidelines do not recommend the routinely use of antibiotic prophylaxis in severe AP patients⁴⁴. Currently, the indications for the use of antibiotic therapy in necrotizing AP include the presence of confirmed pancreatic necrosis after culture of pancreatic collection fluid after FNA and suspected pancreatic necrosis infection^{11,12,23,44}. In the presence of suspected or confirmed pancreatic necrosis infection, it is necessary to evaluate the clinical condition of the patient⁶⁸. Thus, in the case of clinically stable patients, a step-up approach that allows the delay of surgery while utilizing maximal supportive care with close clinical observation in a monitored hospital environment is recommended^{70,71}. Conversely, in the case of clinically unstable patients, prompt surgical debridement of pancreatic necrosis is recommended and these patients should be managed in intensive care units (ICUs)¹². Literature data have demonstrated the clinical efficacy of a carbapenems-based antibiotic prophylaxis that present a trend towards efficacy but without statistical significance^{44,63,72}. Prophylactic antibiotic therapy should be based

on pancreatic-penetrating antibiotics, such as carbapenems (with imipenem as the first line), quinolones or high-dose cephalosporin with metronidazole^{43,68,73}. However, although guidelines recommend the use of antibiotic therapy only in few selected case of necrotizing AP patients, the real-world evidence demonstrates that there is a common and recurrent inappropriate use of antibiotics in several clinical conditions, which do not warrant such treatment⁶². Just as feeding modalities of severe AP patients that have been amended during the last years strongly modifying the old paradigm of the use of parenteral nutrition, we expect these novel clinical data in the use of antibiotic therapy should become more accepted and widely practiced and break down the old knowledge barriers in the management of severe AP. In conclusion, it is important to underline that each case is unique and thus the timing and method of antibiotic treatment should be individualized and based on the patient's clinical condition and preferences, presence of peri-pancreatic and systemic complications, and techniques available in the hospital, leading to optimal personalized treatment.

Pain Control

In the early phase of AP patients, the control of pain represents an important tool in disease management. The pain is constantly present in AP patients, and is utilized as diagnostic criteria. Pain relief is a clinical priority and represents another intriguing and debated point in the clinical setting⁴⁴. Several RCTs and clinical studies^{44,74,75} have been performed to test the efficacy in the management of AP related pain of different drugs, such as opioids, NSAIDs, anesthetics, and others. A systematic review⁷⁶ of several RCTs comparing different analgesics has shown that these studies did not reach an effective demonstration of a real efficacy of a particular class of drugs. Another old paradigm has been changed regarding the use of morphine in treating AP related pain. In fact, it was thought that morphine might cause Oddi sphincter spasm and thus worsen the course of AP. However, clinical evidence has confuted this issue showing that morphine may be useful and safe in the relief of pain in AP patients^{44,74,77}. Another RCT comparing IV paracetamol to two different NSAID and opioid drugs has shown that there is no superiority among them⁷⁵. Finally, if the pain is not well controlled by a high dose opioid therapy, it is possible to utilize epidural analgesia⁴⁴.

Etiology and risk factors management

The prompt recognition of the possible etiology of AP and associated risk factors is essential to start the appropriate etiological therapy¹¹. As reported above, about one-third of all cases of AP are associated with alcohol consumption, and it is necessary to stop its intake once AP is confirmed, immediately. Likewise, in cases of drug-induced AP, it is very important to identify the possible drug involved and stop it³². Moreover, it has been reported that about 40% of AP is associated with stones in the gallbladder and biliary tract that may also cause cholelithiasis- and choledocholithiasis-associated cholangitis. Hence, after excluding alcohol or drug-induced AP, the next step in AP patient assessment is to evaluate the presence of stones in the gallbladder and, in this case, US assessment may be sufficient. To determine the presence of stones in the biliary tract a second level imaging is required. For the evaluation of stones, CT scan is very useful to detect calcified stones, and MRCP may be used to assess the integrity of the biliary tract and to detect the presence of radiotransparent lithiasis. Finally, when choledocholithiasis is strongly suspected and CT and MRCP assessment are inconclusive, there is an indication to perform EUS. There is a wide literature evidence⁷⁸⁻⁸² confirming the pivotal role of EUS in detecting choledocholithiasis, that it may be considered as the diagnostic gold standard. In the case of biliary AP associated with gallstones, guidelines recommend performing cholecystectomy within the same hospitalization in the case of mild AP⁸³, or after 6 weeks, in the case of moderate-severe AP^{11,12,23}.

Then, in the presence of peri-pancreatic inflammatory fluid collections, such as pseudocysts and WONs, a multi-disciplinary approach is required to decide the best timing for cholecystectomy¹². The presence of wide acute and chronic peri-pancreatic collections may be a contraindication for cholecystectomy that should be performed only after the spontaneous resolution of the collections. In the case of peri-pancreatic collections, pseudocysts and WONs associated with abdominal symptoms, therapeutical drainage is required, and it may be EUS-guided, percutaneously, or even through surgical resection, mainly in the cases of infected pancreatic necrosis^{84,85}. In 2010, an important multicenter study⁸⁶ demonstrated that in case of necrotizing AP a minimally invasive 'step-up approach' is the most appropriate choice instead of the traditional open necrosectomy. This evidence has changed the management of severe AP, and EUS-guided

drainage of pseudocysts and WONs has been emerging as the procedure of choice over traditional open surgery⁸⁷⁻⁹². In this way, EUS-guided gastroenterostomy (EUS-GE) may be utilized for the drainage of necrotic peri-pancreatic collections, such as WONs, or even for the drainage of biliary and pancreatic ducts and acute cholecystitis^{93,94}. Then, EUS-GE may be indicated when ERCP fails in accessing and draining the biliary system and the pancreatic duct^{89,93}. Endoscopic procedures are similarly efficacious to surgical procedures, but have the significant advantages of low complication rates, better quality of life and reduced hospitalization time and costs^{4,89,95-98}. In this 'step-up' endoscopic approach, both endoscopic and percutaneous routes may be used, and the decision is related to the anatomical location and morphological features of the collections⁸⁹. Surgery is considered appropriate only in cases of failed EUS- and percutaneous- drainage of peri-pancreatic collections and necrosis^{11,90}. Moreover, in the case of biliary AP associated with stones in the biliary tract, it is necessary to perform ERCP to remove the stones or the biliary sludge that may be related to obstructions and cause cholangitis^{12,99,100}. Guidelines recommend urgent ERCP within 24 hours in patients with acute cholangitis¹⁰¹, but there is no clear evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis¹².

Conclusions

Acute pancreatitis is a potentially life-threatening disease with a wide range of clinical presentation, morbidity, and mortality. Several clinical, laboratoristic and radiological scores have been developed to classify the severity of AP. Predicting the severity of AP is crucial for the management of the disease. The course of severe AP is usually divided in two principal phases. The early phase is mainly characterized by the fluid redistribution and infectious risk related to the activation of auto-inflammatory pancreatic pathway, the subsequent gut dysbiosis and systemic bacterial translocation, and immune system down-regulation, precipitating in the condition of SIRS. In this early phase, AP patients are at risk of sepsis and septic shock. The late phase of severe AP is characterized by the development of local and systemic complications. These two phases are related to the two peaks of morbidity and mortality associated with severe AP. During the last decades, several old paradigms have been

amended in the management of AP patients, such as the indication of nutrition, the use of antibiotic therapy, pain control strategies, and even the use of surgery. Real world evidence has shown that in the large part of cases a multi-disciplinary step-up approach yields better outcomes.

Conflict of Interests

No potential conflicts of interest. No financial support.

References

- 1) JOHNSON CD, BESSELINK MG, CARTER R. Acute pancreatitis. *BMJ* 2014; 349: g4859.
- 2) PAPACHRISTOU GI, MACHICADO JD, STEVENS T, GOENKA MK, FERREIRA M, GUTIERREZ SC, SINGH VK, KAMAL A, GONZALEZ-GONZALEZ JA, PELAEZ-LUNA M, GULLA A, ZARNESCU NO, TRIANTAFYLLOU K, BARBU ST, EASLER J, OCAMPO C, CAPURSO G, ARCHIBUGI L, COTE GA, LAMBIASE L, KOCHHAR R, CHUA T, TIWARI SC, NAWAZ H, PARK WG, DE-MADARIA E, LEE PJ, WU BU, GREER PJ, DUGUM M, KOUTROUMPAKIS E, AKSHINTALA V, GOUGOL A. Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE): an international, multicenter consortium for the study of acute pancreatitis. *Ann Gastroenterol* 2017; 30: 106-113.
- 3) YADAV D, LOWENFELS AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; 144: 1252-1261.
- 4) WU BU, BANKS PA. Clinical management of patients with acute pancreatitis. *Gastroenterology* 2013; 144: 1272-1281.
- 5) BANKS PA, BOLLEN TL, DERVENIS C, GOOSZEN HG, JOHNSON CD, SARR MG, TSIOTOS GG, VEGE SS, ACUTE PANCREATITIS CLASSIFICATION WORKING G. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102-111.
- 6) QUINLAN JD. Acute pancreatitis. *Am Fam Physician* 2014; 90: 632-639.
- 7) DOUROS A, BRONDER E, ANDERSON F, KLIMPEL A, THOMAE M, OCKENGA J, KREUTZ R, GARBE E. Drug-induced acute pancreatitis: results from the hospital-based Berlin case-control surveillance study of 102 cases. *Aliment Pharmacol Ther* 2013; 38: 825-834.
- 8) ALESSANDRI G, AMODIO A, LANDONI L, DE' LIGUORI CARINO N, BASSI C. Recurrent acute pancreatitis in bowel malrotation. *Eur Rev Med Pharmacol Sci* 2016; 20: 4719-4724.
- 9) FORSMARK CE, VEGE SS, WILCOX CM. Acute pancreatitis. *N Engl J Med* 2016; 375: 1972-1981.
- 10) BOLLEN TL, SINGH VK, MAURER R, REPAS K, VAN ES HW, BANKS PA, MORTELE KJ. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. *Am J Gastroenterol* 2012; 107: 612-619.
- 11) TENNER S, BAILLIE J, DEWITT J, VEGE SS, AMERICAN COLLEGE OF G. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; 108: 1400-1415; 1416.
- 12) WORKING GROUP IAP/APA ACUTE PANCREATITIS GUIDELINES. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; 13: e1-15.
- 13) FOSTER BR, JENSEN KK, BAKIS G, SHAABAN AM, COAKLEY FV. Revised Atlanta Classification for Acute Pancreatitis: a pictorial essay. *Radiographics* 2016; 36: 675-687.
- 14) JOHNSON CD, ABU-HILAL M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004; 53: 1340-1344.
- 15) MOFIDI R, DUFF MD, WIGMORE SJ, MADHAVAN KK, GARDEN OJ, PARKS RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg* 2006; 93: 738-744.
- 16) PETROV MS, SHANBHAG S, CHAKRABORTY M, PHILLIPS AR, WINDSOR JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010; 139: 813-820.
- 17) SARR MG, BANKS PA, BOLLEN TL, DERVENIS C, GOOSZEN HG, JOHNSON CD, TSIOTOS GG, VEGE SS. The new revised classification of acute pancreatitis 2012. *Surg Clin North Am* 2013; 93: 549-562.
- 18) SMOTKIN J, TENNER S. Laboratory diagnostic tests in acute pancreatitis. *J Clin Gastroenterol* 2002; 34: 459-462.
- 19) TENNER SM, STEINBERG W. The admission serum lipase:amylase ratio differentiates alcoholic from nonalcoholic acute pancreatitis. *Am J Gastroenterol* 1992; 87: 1755-1758.
- 20) YADAV D, AGARWAL N, PITCHUMONI CS. A critical evaluation of laboratory tests in acute pancreatitis. *Am J Gastroenterol* 2002; 97: 1309-1318.
- 21) BANKS PA, FREEMAN ML. Practice Parameters Committee of the American College of G. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; 101: 2379-2400.
- 22) YANG CJ, CHEN J, PHILLIPS AR, WINDSOR JA, PETROV MS. Predictors of severe and critical acute pancreatitis: a systematic review. *Dig Liver Dis* 2014; 46: 446-451.
- 23) PEZZILLI R, ZERBI A, DI CARLO V, BASSI C, DELLE FAVE GF, WORKING GROUP OF THE ITALIAN ASSOCIATION FOR THE STUDY OF THE PANCREAS ON ACUTE P. Practical guidelines for acute pancreatitis. *Pancreatology* 2010; 10: 523-535.
- 24) KHANNA AK, MEHER S, PRAKASH S, TIWARY SK, SINGH U, SRIVASTAVA A, DIXIT VK. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. *HPB Surg* 2013; 2013: 367581.
- 25) PAPACHRISTOU GI, MUDDANA V, YADAV D, O'CONNELL M, SANDERS MK, SLIVKA A, WHITCOMB DC. Comparison of

- BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol* 2010; 105: 435-441; quiz 442.
- 26) DERVENIS C, JOHNSON CD, BASSI C, BRADLEY E, IMRIE CW, McMAHON MJ, MODLIN I. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini consensus conference. *Int J Pancreatol* 1999; 25: 195-210.
 - 27) O'CONNOR OJ, McWILLIAMS S, MAHER MM. Imaging of acute pancreatitis. *AJR Am J Roentgenol* 2011; 197: W221-225.
 - 28) BALTHAZAR EJ, ROBINSON DL, MEGIBOW AJ, RANSON JH. Acute pancreatitis: value of CT in establishing prognosis. *Radiology* 1990; 174: 331-336.
 - 29) PAGLIARI D, SAVIANO A, SERRICCHIO ML, DAL LAGO AA, BRIZI MG, LANZA F, MANFREDI R, GASBARRINI A, ATTILI F. Uptodate in the assessment and management of intraductal papillary mucinous neoplasms of the pancreas. *Eur Rev Med Pharmacol Sci* 2017; 21: 2858-2874.
 - 30) STIMAC D, MILETIC D, RADIC M, KRZANARIC I, MAZUR-GRBAC M, PERKOVIC D, MILIC S, GOLUBOVIC V. The role of nonenhanced magnetic resonance imaging in the early assessment of acute pancreatitis. *Am J Gastroenterol* 2007; 102: 997-1004.
 - 31) TAYLOR AC, LITTLE AF, HENNESSY OF, BANTING SW, SMITH PJ, DESMOND PV. Prospective assessment of magnetic resonance cholangiopancreatography for noninvasive imaging of the biliary tree. *Gastrointest Endosc* 2002; 55: 17-22.
 - 32) PHILLIP V, STEINER JM, ALGUL H. Early phase of acute pancreatitis: assessment and management. *World J Gastrointest Pathophysiol* 2014; 5: 158-168.
 - 33) CIANCI R, SPADA C, PERRI V, CAMMAROTA G, URGESI R, LOLLI S, GIRARDI E, COSTAMAGNA G, PANDOLFI F. Active thymopoiesis in idiopathic chronic pancreatitis. *Eur Rev Med Pharmacol Sci* 2008; 12: 41-46.
 - 34) ZHANG MS, ZHANG KJ, ZHANG J, JIAO XL, CHEN D, ZHANG DL. Phospholipases A-II (PLA2-II) induces acute pancreatitis through activation of the transcription factor NF-kappaB. *Eur Rev Med Pharmacol Sci* 2014; 18: 1163-1169.
 - 35) TIAN R, TAN JT, WANG RL, XIE H, QIAN YB, YU KL. The role of intestinal mucosa oxidative stress in gut barrier dysfunction of severe acute pancreatitis. *Eur Rev Med Pharmacol Sci* 2013; 17: 349-355.
 - 36) LESER HG, GROSS V, SCHEIBENBOGEN C, HEINISCH A, SALM R, LAUSEN M, RUCKAUER K, ANDRESEN R, FARTHMAN EH, SCHOLMERICH J. Elevation of serum interleukin-6 concentration precedes acute-phase response and reflects severity in acute pancreatitis. *Gastroenterology* 1991; 101: 782-785.
 - 37) PAGLIARI D, SAVIANO A, NEWTON EE, SERRICCHIO ML, DAL LAGO AA, GASBARRINI A, CIANCI R. Gut microbiota-immune system crosstalk and pancreatic disorders. *Mediators Inflamm* 2018; 2018: 7946431.
 - 38) JIN Y, XU H, CHEN Y, WU J, JIN F, WU Q, YAO XM. Therapeutic effect of Bifidobacterium combined with early enteral nutrition in the treatment of severe acute pancreatitis: a pilot study. *Eur Rev Med Pharmacol Sci* 2018; 22: 4018-4024.
 - 39) SUNKARA T, ETIENNE D, CAUGHEY ME, GADUPUTI V. Small bowel obstruction secondary to acute pancreatitis. *Gastroenterology Res* 2017; 10: 42-44.
 - 40) GREENBERG JA, HSU J, BAWAZEER M, MARSHALL J, FRIEDRICH JO, NATHENS A, COBURN N, MAY GR, PEARSALL E, McLEOD RS. Clinical practice guideline: management of acute pancreatitis. *Can J Surg* 2016; 59: 128-140.
 - 41) GUO H, SUO DW, ZHU HP, SUN XM, CHEN J. Early blood purification therapy of severe acute pancreatitis complicated by acute lung injury. *Eur Rev Med Pharmacol Sci* 2016; 20: 873-878.
 - 42) LIM CL, LEE W, LIEW YX, TANG SS, CHLEBICKI MP, KWA AL. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. *J Gastrointest Surg* 2015; 19: 480-491.
 - 43) MOGGIA E, KOTI R, BELGAUMKAR AP, FAZIO F, PEREIRA SP, DAVIDSON BR, GURUSAMY KS. Pharmacological interventions for acute pancreatitis. *Cochrane Database Syst Rev* 2017; 4: CD011384.
 - 44) STIGLIANO S, STERNBY H, DE MADARIA E, CAPURSO G, PETROV MS. Early management of acute pancreatitis: a review of the best evidence. *Dig Liver Dis* 2017; 49: 585-594.
 - 45) ANDRIULLI A, LEANDRO G, CLEMENTE R, FESTA V, CARUSO N, ANNESE V, LEZZI G, LICHINO E, BRUNO F, PERRI F. Meta-analysis of somatostatin, octreotide and gabexate mesilate in the therapy of acute pancreatitis. *Aliment Pharmacol Ther* 1998; 12: 237-245.
 - 46) XU W, ZHOU YF, XIA SH. Octreotide for primary moderate to severe acute pancreatitis: a meta-analysis. *Hepatogastroenterology* 2013; 60: 1504-1508.
 - 47) HAYDOCK MD, MITTAL A, WILMS HR, PHILLIPS A, PETROV MS, WINDSOR JA. Fluid therapy in acute pancreatitis: anybody's guess. *Ann Surg* 2013; 257: 182-188.
 - 48) ITALIAN ASSOCIATION FOR THE STUDY OF THE PANCREAS, PEZZILLI R, ZERBI A, CAMPRA D, CAPURSO G, GOLFIERI R, ARCIDIACONO PG, BILLI P, BUTTURINI G, CALCULLI L, CANNIZZARO R, CARRARA S, CRIPPA S, DE GAUDIO R, DE RAI P, FRULLONI L, MAZZA E, MUTIGNANI M, PAGANO N, RABITTI P, BALZANO G. Consensus guidelines on severe acute pancreatitis. *Dig Liver Dis* 2015; 47: 532-543.
 - 49) MAO EO, FEI J, PENG YB, HUANG J, TANG YQ, ZHANG SD. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. *Chin Med J (Engl)* 2010; 123: 1639-1644.
 - 50) WU BU, HWANG JQ, GARDNER TH, REPAS K, DELEE R, YU S, SMITH B, BANKS PA, CONWELL DL. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 2011; 9: 710-717 e711.
 - 51) BORTOLOTTI P, SAULNIER F, COLLING D, REDHEUIL A, PREAU S. New tools for optimizing fluid resuscitation in acute pancreatitis. *World J Gastroenterol* 2014; 20: 16113-16122.

- 52) PENG T, PENG X, HUANG M, CUI J, ZHANG Y, WU H, WANG C. Serum calcium as an indicator of persistent organ failure in acute pancreatitis. *Am J Emerg Med* 2017; 35: 978-982.
- 53) RINNINELLA E, ANNETTA MG, SERRICCHIO ML, DAL LAGO AA, MIGGIANO GA, MELE MC. Nutritional support in acute pancreatitis: from physiopathology to practice. An evidence-based approach. *Eur Rev Med Pharmacol Sci* 2017; 21: 421-432.
- 54) OLAH A, ROMICS L, JR. Enteral nutrition in acute pancreatitis: a review of the current evidence. *World J Gastroenterol* 2014; 20: 16123-16131.
- 55) LI JY, YU T, CHEN GC, YUAN YH, ZHONG W, ZHAO LN, CHEN QK. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. *PLoS One* 2013; 8: e64926.
- 56) SUN JK, MU XW, LI WQ, TONG ZH, LI J, ZHENG SY. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World J Gastroenterol* 2013; 19: 917-922.
- 57) BAKKER OJ, VAN BRUNSCHOT S, FARRE A, JOHNSON CD, KALFARENTZOS F, LOUIE BE, OLAH A, O'KEEFE SJ, PETROV MS, POWELL JJ, BESSELINK MG, VAN SANTVOORT HC, ROVERS MM, GOOSZEN HG. Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. *Pancreatol* 2014; 14: 340-346.
- 58) STIMAC D, POROPAT G, HAUSER G, LICUL V, FRANJIC N, VALKOVIC ZUJIC P, MILIC S. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: a randomized clinical trial. *Pancreatol* 2016; 16: 523-528.
- 59) BAKKER OJ, VAN BRUNSCHOT S, VAN SANTVOORT HC, BESSELINK MG, BOLLEN TL, BOERMEESTER MA, DEJONG CH, VAN GOOR H, BOSSCHA K, AHMED ALI U, BOUWENSE S, VAN GREVENSTEIN WM, HEISTERKAMP J, HOUDIJK AP, JANSEN JM, KARSTEN TM, MANUSAMA ER, NIEUWENHUIJS VB, SCHAAPHERDER AF, VAN DER SCHELLING GP, SCHWARTZ MP, SPANIER BW, TAN A, VECHT J, WEUSTEN BL, WITTEMAN BJ, AKKERMANS LM, BRUNO MJ, DIJKGRAAF MG, VAN RAMSHORST B, GOOSZEN HG, DUTCH PANCREATITIS STUDY G. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* 2014; 371: 1983-1993.
- 60) EVANS RP, MOURAD MM, PALL G, FISHER SG, BRAMHALL SR. Pancreatitis: preventing catastrophic haemorrhage. *World J Gastroenterol* 2017; 23: 5460-5468.
- 61) ZEREM E. Treatment of severe acute pancreatitis and its complications. *World J Gastroenterol* 2014; 20: 13879-13892.
- 62) KOUTROUMPAKIS E, SLIVKA A, FURLAN A, DASYAM AK, DUDEKULA A, GREER JB, WHITCOMB DC, YADAV D, PAPACHRISTOU GI. Management and outcomes of acute pancreatitis patients over the last decade: a US tertiary-center experience. *Pancreatol* 2017; 17: 32-40.
- 63) PEDERZOLI P, BASSI C, VESENTINI S, CAMPEDELLI A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surg Gynecol Obstet* 1993; 176: 480-483.
- 64) DE VRIES AC, BESSELINK MG, BUSKENS E, RIDWAN BU, SCHIPPER M, VAN ERPECUM KJ, GOOSZEN HG. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. *Pancreatol* 2007; 7: 531-538.
- 65) DELLINGER EP, TELLADO JM, SOTO NE, ASHLEY SW, BARIE PS, DUGERNIER T, IMRIE CW, JOHNSON CD, KNAEBEL HP, LATERRE PF, MARAVI-POMA E, KISSLER JJ, SANCHEZ-GARCIA M, UTZOLINO S. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Ann Surg* 2007; 245: 674-683.
- 66) VILLATORO E, MULLA M, LARVIN M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2010: CD002941.
- 67) DE CAMPOS T, ASSEF JC, RASSLAN S. Questions about the use of antibiotics in acute pancreatitis. *World J Emerg Surg* 2006; 1: 20.
- 68) ZAVYALOV T, KHOTSZYNA Y, TENNER S. The role of antibiotics in the management of patients with acute necrotizing pancreatitis. *Curr Infect Dis Rep* 2010; 12: 13-18.
- 69) MOURAD MM, EVANS R, KALIDINDI V, NAVARATNAM R, DVORKIN L, BRAMHALL SR. Prophylactic antibiotics in acute pancreatitis: endless debate. *Ann R Coll Surg Engl* 2017; 99: 107-112.
- 70) GARG PK, SHARMA M, MADAN K, SAHNI P, BANERJEE D, GOYAL R. Primary conservative treatment results in mortality comparable to surgery in patients with infected pancreatic necrosis. *Clin Gastroenterol Hepatol* 2010; 8: 1089-1094 e1082.
- 71) SORRENTINO L, CHIARA O, MUTIGNANI M, SAMMARTANO F, BRIOSCHI P, CIMBANASSI S. Combined totally mini-invasive approach in necrotizing pancreatitis: a case report and systematic literature review. *World J Emerg Surg* 2017; 12: 16.
- 72) ISENMANN R, RUNZI M, KRON M, KAHL S, KRAUS D, JUNG N, MAIER L, MALFERTHEINER P, GOEBELL H, BEGER HG, GERMAN ANTIBIOTICS IN SEVERE ACUTE PANCREATITIS STUDY G. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology* 2004; 126: 997-1004.
- 73) MARAVI-POMA E, GENER J, ALVAREZ-LERMA F, OLAECHEA P, BLANCO A, DOMINGUEZ-MUNOZ JE, SPANISH GROUP FOR THE STUDY OF SEPTIC COMPLICATIONS IN SEVERE ACUTE P. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. *Intensive Care Med* 2003; 29: 1974-1980.
- 74) BASURTO ONA X, RIGAU COMAS D, URRUTIA G. Opioids for acute pancreatitis pain. *Cochrane Database Syst Rev* 2013: CD009179.
- 75) GULEN B, DUR A, SERINKEN M, KARCIOGLU O, SONMEZ E. Pain treatment in patients with acute pancreatitis: A randomized controlled trial. *Turk J Gastroenterol* 2016; 27: 192-196.

- 76) MENG W, YUAN J, ZHANG C, BAI Z, ZHOU W, YAN J, LI X. Parenteral analgesics for pain relief in acute pancreatitis: a systematic review. *Pancreatology* 2013; 13: 201-206.
- 77) BLAMEY SL, FINLAY IG, CARTER DC, IMRIE CW. Analgesia in acute pancreatitis: comparison of buprenorphine and pethidine. *Br Med J (Clin Res Ed)* 1984; 288: 1494-1495.
- 78) CHAK A, HAWES RH, COOPER GS, HOFFMAN B, CATALANO MF, WONG RC, HERBENER TE, SIVAK MV, JR. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. *Gastrointest Endosc* 1999; 49: 599-604.
- 79) ANDERLONI A, GALEAZZI M, BALLARE M, PAGLIARULO M, ORSELLO M, DEL PIANO M, REPICI A. Early endoscopic ultrasonography in acute biliary pancreatitis: a prospective pilot study. *World J Gastroenterol* 2015; 21: 10427-10434.
- 80) DE LISI S, LEANDRO G, BUSCARINI E. Endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography in acute biliary pancreatitis: a systematic review. *Eur J Gastroenterol Hepatol* 2011; 23: 367-374.
- 81) SOTOUDEHMANESH R, HOOSHYAR A, KOLAHDOOZAN S, ZEINALI F, SHAHRAEENI S, KESHTKAR AA. Prognostic value of endoscopic ultrasound in acute pancreatitis. *Pancreatology* 2010; 10: 702-706.
- 82) VAN SANTVOORT HC, BAKKER OJ, BESSELINK MG, BOLLEN TL, FISCHER K, NIEUWENHUIJS VB, GOOSZEN HG, ERPECUM KJ, DUTCH PANCREATITIS STUDY G. Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. *Endoscopy* 2011; 43: 8-13.
- 83) DA COSTA DW, BOUWENSE SA, SCHEPERS NJ, BESSELINK MG, VAN SANTVOORT HC, VAN BRUNSCHOT S, BAKKER OJ, BOLLEN TL, DEJONG CH, VAN GOOR H, BOERMEESTER MA, BRUNO MJ, VAN EIJCK CH, TIMMER R, WEUSTEN BL, CONSTEN EC, BRINK MA, SPANIER BWM, BILGEN EJS, NIEUWENHUIJS VB, HOFKER HS, ROSMAN C, VOORBURG AM, BOSSCHA K, VAN DUUVENDIJK P, GERITSSEN JJ, HEISTERKAMP J, DE HINGH IH, WITTEMAN BJ, KRUYT PM, SCHEEPERS JJ, MOLENAAR IQ, SCHAAPHERDER AF, MANUSAMA ER, VAN DER WAAIJ LA, VAN UNEN J, DIJKGRAAF MG, VAN RAMSHORST B, GOOSZEN HG, BOERMA D, DUTCH PANCREATITIS STUDY G. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet* 2015; 386: 1261-1268.
- 84) CUI ML, KIM KH, KIM HG, HAN J, KIM H, CHO KB, JUNG MK, CHO CM, KIM TN. Incidence, risk factors and clinical course of pancreatic fluid collections in acute pancreatitis. *Dig Dis Sci* 2014; 59: 1055-1062.
- 85) VAN SANTVOORT HC, BAKKER OJ, BOLLEN TL, BESSELINK MG, AHMED ALI U, SCHRIJVER AM, BOERMEESTER MA, VAN GOOR H, DEJONG CH, VAN EIJCK CH, VAN RAMSHORST B, SCHAAPHERDER AF, VAN DER HARST E, HOFKER S, NIEUWENHUIJS VB, BRINK MA, KRUYT PM, MANUSAMA ER, VAN DER SCHELLING GP, KARSTEN T, HESSELINK EJ, VAN LAARHOVEN CJ, ROSMAN C, BOSSCHA K, DE WIT RJ, HOUDIJK AP, CUESTA MA, WAHAB PJ, GOOSZEN HG, DUTCH PANCREATITIS STUDY G. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011; 141: 1254-1263.
- 86) ZEREM E, HAUSER G, LOGA-ZEC S, KUNOSIC S, JOVANOVIĆ P, CRNKIĆ D. Minimally invasive treatment of pancreatic pseudocysts. *World J Gastroenterol* 2015; 21: 6850-6860.
- 87) RANA SS, SHARMA V, SHARMA R, GUPTA R, BHASIN DK. Endoscopic ultrasound guided transmural drainage of walled off pancreatic necrosis using a "step - up" approach: a single centre experience. *Pancreatology* 2017; 17: 203-208.
- 88) SHAH A, DENICOLA R, EDIRISURIYA C, SIDDIQUI AA. Management of inflammatory fluid collections and walled-off pancreatic necrosis. *Curr Treat Options Gastroenterol* 2017; 15: 576-586.
- 89) YIP HC, TEOH AYB. Endoscopic management of peri-pancreatic fluid collections. *Gut Liver* 2017; 11: 604-611.
- 90) BAKKER OJ, VAN SANTVOORT HC, VAN BRUNSCHOT S, GESKUS RB, BESSELINK MG, BOLLEN TL, VAN EIJCK CH, FOCKENS P, HAZEBROEK EJ, NIJMEIJER RM, POLEY JW, VAN RAMSHORST B, VLEGGAAR FP, BOERMEESTER MA, GOOSZEN HG, WEUSTEN BL, TIMMER R, DUTCH PANCREATITIS STUDY G. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; 307: 1053-1061.
- 91) VAN GRINSVEN J, VAN SANTVOORT HC, BOERMEESTER MA, DEJONG CH, VAN EIJCK CH, FOCKENS P, BESSELINK MG, DUTCH PANCREATITIS STUDY G. Timing of catheter drainage in infected necrotizing pancreatitis. *Nat Rev Gastroenterol Hepatol* 2016; 13: 306-312.
- 92) VAN SANTVOORT HC, BESSELINK MG, BAKKER OJ, HOFKER HS, BOERMEESTER MA, DEJONG CH, VAN GOOR H, SCHAAPHERDER AF, VAN EIJCK CH, BOLLEN TL, VAN RAMSHORST B, NIEUWENHUIJS VB, TIMMER R, LAMERIS JS, KRUYT PM, MANUSAMA ER, VAN DER HARST E, VAN DER SCHELLING GP, KARSTEN T, HESSELINK EJ, VAN LAARHOVEN CJ, ROSMAN C, BOSSCHA K, DE WIT RJ, HOUDIJK AP, VAN LEEUWEN MS, BUSKENS E, GOOSZEN HG, DUTCH PANCREATITIS STUDY G. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; 362: 1491-1502.
- 93) RIMBAS M, LARGHI A. Endoscopic ultrasonography-guided techniques for accessing and draining the biliary system and the pancreatic duct. *Gastrointest Endosc Clin N Am* 2017; 27: 681-705.
- 94) RIMBAS M, LARGHI A, COSTAMAGNA G. Endoscopic ultrasound-guided gastroenterostomy: Are we ready for prime time? *Endosc Ultrasound* 2017; 6: 235-240.
- 95) VARADARAJULU S, CHRISTEIN JD, TAMHANE A, DRELICHMAN ER, WILCOX CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; 68: 1102-1111.

- 96) GERIN O, PREVOT F, DHAHRI A, HAKIM S, DELCENSERIE R, REBIBO L, REGIMBEAU JM. Laparoscopy-assisted open cystogastrostomy and pancreatic debridement for necrotizing pancreatitis (with video). *Surg Endosc* 2016; 30: 1235-1241.
- 97) HAO SJ, XU WJ, DI Y, YAO L, HE H, YANG F, JIN C, ZHONG L, FU DL. Novel and supplementary management of pancreatic fluid collections: endoscopic ultrasound-guided drainage. *World J Gastrointest Endosc* 2017; 9: 486-493.
- 98) BRUGGE WR. Diagnosis and management of cystic lesions of the pancreas. *J Gastrointest Oncol* 2015; 6: 375-388.
- 99) TSE F, YUAN Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev* 2012: CD009779.
- 100) FROSSARD JL, SPAHR L. ERCP for gallstone pancreatitis. *N Engl J Med* 2014; 370: 1954-1955.
- 101) CROCKETT SD, WANI S, GARDNER TB, FALCK-YTTER Y, BARKUN AN, AMERICAN GASTROENTEROLOGICAL ASSOCIATION INSTITUTE CLINICAL GUIDELINES C. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology* 2018; 154: 1096-1101.