Chapter

Management of Acute and Chronic Pancreatitis

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Abstract

Pancreatitis is a major public health issue worldwide. There is geographical variation in the burden of acute and chronic pancreatitis (CP). Globally, the age-standardized prevalence rate increased from 1990 to 2017. Acute pancreatitis (AP) is now one of the most common reasons for hospitalization with a gastrointestinal condition. The essential requirements for the management of AP are accurate diagnosis, appropriate triage, high-quality supportive care, monitoring for and treatment of complications, and prevention of relapse. Clinicians should be aware of the time course and the best management of AP, identifying which patient will have a severe course allowing earlier triage to an intensive care unit and earlier initiation of effective therapy. CP is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and other risk factors who develop persistent pathologic responses to parenchymal injury or stress. Diagnosing the underlying pathologic process early in the disease course and managing the syndrome to change the natural course of disease and minimize adverse disease effects are the managing paradigm. In this review, we consider recent changes in the management of acute and CP, as well as common misunderstandings and areas of ongoing controversy.

Keywords: acute pancreatitis, chronic pancreatitis, management, clinical phases, pathologic process

1. Introduction

Pancreatitis is a major public health issue worldwide. There is geographical variation in the burden of acute and chronic pancreatitis (CP). Globally, the age-standardized prevalence rate increased from 1990 to 2017. Acute pancreatitis (AP) is now one of the most common reasons for hospitalization with a gastrointestinal condition. The essential requirements for the management of AP are accurate diagnosis, appropriate triage, high-quality supportive care, monitoring for and treatment of complications, and prevention of relapse. Clinicians should be aware of the time course and the best management of AP, identifying which patient will have a severe course allowing earlier triage to an intensive care unit and earlier initiation of effective

therapy. CP is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and other risk factors who develop persistent pathologic responses to parenchymal injury or stress. Diagnosing the underlying pathologic process early in the disease course and managing the syndrome to change the natural course of disease and minimize adverse disease effects is the managing paradigm. In this review, we consider recent changes in the management of acute and CP, as well as common misunderstandings and areas of ongoing controversy.

Current concepts of the use of interventional methods in severe acute, necrotizing, and CP (indications and timing of interventions, strategies for intervention, endoscopic and percutaneous treatment) are discussed in the other chapters of this monograph on pancreatitis. We, therefore, consider it appropriate that they are illustrated in detail in the respective chapters.

2. Acute pancreatitis

AP is an acute inflammatory condition of the pancreas with histological acinar cells destruction. It has a wide spectrum of morphological and clinical manifestations and can result in local injury, systemic inflammatory response syndrome (SIRS) and organ failure [1, 2].

2.1 Epidemiology

AP is one of the most common gastrointestinal diseases requiring acute hospitalization [3]. Its incidence is rising worldwide and ranges from 5 to 30 cases per 100,000 [1] and despite improvements in the diagnosis, management and treatment, the overall mortality rate of AP remains around 2–5% [4, 5]. The average length of hospital stay for AP is 8 days, with economic burden to patients and the health care system all around the world [6].

2.2 Etiology

The most common causes of AP are gallstones (up to 40–70% of cases) and alcohol abuse (25–35%).

Migrating gallstones cause transient obstruction of the pancreatic duct leading to the blockage of pancreatic secretion and lysosomal dysfunction generating injury and inflammatory response. Alcohol abuse exerts its effects in a complex way that include direct toxicity and immunologic mechanisms: prolonged alcohol use (four to five drinks in a day over a period of more than 5 years) is required and the type of alcohol ingested does not affect the overall lifetime risk of alcohol-associated pancreatitis, that range from 2% to 5% in heavy drinkers ("Heavy" alcohol consumption is generally considered to be >50 g in a day).

In absence of gallstones or alcohol, other etiologies of AP (**Table 1**) must be ruled out.

The agent or condition causing AP is not always clear and sometimes there is only the evidence of factors known to be potential contributors of unexplained pancreatitis, such as smoke, obesity and diabetes. Accordingly, idiopathic AP has been defined as a condition in which the etiological cause is not detectable after an accurate anamnesis excluding any substance abuse, infections, metabolic disorders, genetic mutations and at least two second-level imaging techniques [endoscopic ultrasound and

Cause	Frequency	Notes
Gallstones	40%	Gallbladder stones or sludge
Alcohol	25–35%	Usually an acute flares on underlying chronic pancreatitis
Drugs	<5%	Most strongly associated: azathioprine, 6-mercaptopurine, dideoxyinosine, valproic acid, angiotensin-converting-enzyme inhibitors, mesalamine
Hypertriglyceridemia	1–5%	Triglyceride level > 10 mmol/l (>1000 mg/dl)
Hypercalcemia		Total serum calcium concentration > 2.60 mmol/l
Autoimmune causes	<1%	Autoimmune pancreatitis (AIP), type 1 or type 2
Genetic causes	Not known	Mutations and polymorphisms in different genes encoding cationic trypsinogen (PRSS1), serine protease inhibitor Kazal type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsin C, calcium-sensing receptor
Endoscopic Retrograde CholangioPancreatography (ERCP)	5–10%*	
Trauma	<1%	Blunt or penetrating trauma
Infections	<1%	CMV, mumps, EBV
Tumors		Malignant tumor of ampulla, distal choledocus or pancreatic head**
Other causes of obstruction	Rare	Pancreas divisum, sphincter of Oddi dysfunction, any benign or malignant mass that obstructs the main pancreatic duct**
Other conditions, unknow	Common	Diabetes, obesity, smoking

Among patients undergoing ERCP.5–14% of patients with benign or malignant pancreatobiliary tumors present with AP.*

Table 1.
Causes of acute pancreatitis.

magnetic resonance imaging (MRI)] to exclude abnormality of pancreatic gland, pancreatic or biliary and gallbladder lithiasis.

Any mass that obstructs the main pancreatic duct can cause AP: 5–14% of patients with benign or malignant pancreatobiliary tumors present with this scenario and pancreatic tumor should be suspected in any patient older than 40 years with idiopathic pancreatitis, especially those with prolonged or recurrent course [4–6].

2.3 Clinical signs and symptoms

Patients with AP usually present with epigastric or left upper quadrant pain, usually described as persistent, severe and often radiating to the back, chest or flanks. The intensity of pain is not correlated to the severity of the disease. Patients experience pain relief when sitting forward or worsening when lying flat. Nausea and vomiting are also common, and sequestered fluid in the small bowel may lead to rapid and severe dehydration. Diaphragmatic irritation may cause hiccoughs. The presentation can also be dominated by shock with tachycardia, tachypnea, hypotension, anuria and mental status alteration. On the other hand, patients may be paucisymptomatic,

with few physical signs. Abdominal examination reveals epigastric tenderness and guarding; abdominal distension with paralytic ileus. Later signs may include mottled skin or livedo reticularis and lace-like purplish discoloration of the skin. Abdominal periumbilical ecchymosis (Cullen's sign) and ecchymosis of the flank (Grey Turner's sign) result from the diffusion of fat necrosis and inflammation associated with retroperitoneal or intra-abdominal bleeding [5].

2.4 Diagnosis

The diagnosis of AP is made following the Revised Atlanta Criteria, a global consensus classification (generated in 1992 and revised in 2012) designed to standardize diagnosis, clinical assessment, evaluation, severity and complications of AP and to help the communication between clinicians.

Diagnosis of AP requires two of the following three features:

- *abdominal pain consistent with AP*;
- *serum lipase or amylase levels at least three times greater than the upper limit of normal range*;
- *characteristic findings of AP on imaging* [contrast-enhanced computed tomography (CT) and less commonly MRI or transabdominal ultrasonography].

According to these criteria, it is important to underline that when the diagnosis of AP is established by abdominal pain and by increased serum pancreatic enzyme activities (clinical and laboratory criteria), the radiological findings (imaging criteria) are not required for making the diagnosis [3, 7].

In the majority of patients, routine use of CT or MRI is unwarranted as the diagnosis of AP is apparent and most have a mild, uncomplicated course. CT or MRI imaging should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48–72 hours after hospital admission [6].

Contrarily, transabdominal ultrasound should be performed on admission in all patients with AP, to define the underlying etiology and to identify the presence of gallstones that are the most common cause of AP [3, 6].

Moreover, it is important to record the time interval between onset, first observation and hospital admission. In fact, the onset of AP is defined as the time of beginning of abdominal pain and not the time of admission to the hospital [7].

In an episode of AP, the enzyme secreted by the pancreas (amylase, lipase, elastase and trypsin) are released from acinar cells of the pancreas into the bloodstream at the same time, due to increased permeability following inflammation.

Amylase is an enzyme synthesized mostly by pancreatic acinar cells and salivary glands and in negligible levels by adipose tissue, gonads, fallopian tubes, intestinal tract and skeletal muscle. Humans product one specific isoenzyme, α-amylase, with two major isoforms specific to pancreas and to salivary glands that help to identify different cases of hyperamylasemia. In case of AP, serum amylase rises rapidly within a few hours after the onset, with peaks at 3–6 hours, half-life of 10–12 hours, persistent elevation for 3–5 days and decrease to normal levels over the next three to 7 days.

Lipase is an enzyme that has a higher specificity because is mainly produced by acinar cells of the pancreas; nevertheless, high serum level can be determined also in patient with renal insufficiency, appendicitis, diabetic ketoacidosis, inflammatory

bowel disease and intestinal obstruction. In AP, elevation of serum lipase arises within three to 6 hours with peaks at 24 hours following the onset of symptoms and persistent elevation up to 2 weeks, giving a larger diagnostic window in comparison to amylase.

Therefore, serum lipase appears to be more specific and remains elevated for a longer period than serum amylase after disease presentation. Moreover, lipase has a better degree of sensitivity and specificity in diagnosing AP, during both early and late phases of the disease (sensitivity of lipase and amylase tests ranges between 64–100% and 45–87%, respectively).

According to these evidences, current guidelines recommend the preference use of serum lipase for diagnosis of AP [2, 4, 6].

2.5 Classification

The most commonly used classification system for AP is the "2012 revision of the Atlanta Classification and definitions" based on international consensus [8].

This classification identifies two types (Interstitial edematous pancreatitis and necrotizing pancreatitis), three grades of severity (mild, moderately severe or severe) and two phases (early and late) of AP.

2.5.1 Types of acute pancreatitis

Two different types of AP have been characterized: Interstitial edematous pancreatitis and necrotizing pancreatitis.

Interstitial edematous pancreatitis is an acute inflammation of pancreatic parenchyma and peri-pancreatic tissues, but without recognizable tissue necrosis. Developed by the majority of patients (80–85%), it is characterized by diffuse (or occasionally localized) enlargement of the pancreas, due to inflammatory edema; the clinical symptoms usually resolve within the first week.

Necrotizing pancreatitis is, instead, the presence of inflammation associated with pancreatic parenchymal necrosis and/or peri-pancreatic necrosis. The natural history of necrotizing pancreatitis is variable and this scenario evolves over several days because necrosis can remain solid or liquefy, can remain sterile or become infected, persist or disappear over time. This explains why an early CT made for assessment of AP may underestimate the eventual extent of pancreatic and peri-pancreatic necrosis. Moreover, most evidence suggest no correlation between the extent of necrosis and the risk of infection and duration of symptoms and usually infected necrosis is rare during the first week. Developed by 15–20% of patients with AP, this type of evolution of AP has increased morbidity and mortality compared to patients with interstitial edematous pancreatitis [5, 7].

2.5.2 Severity of acute pancreatitis

A preliminary overview of complications of AP is mandatory, because the comprehension of these terminologies is central to definition and stratification of severity.

- **Local complications**: acute peri-pancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection (sterile or infected), walled of necrosis (sterile or infected), gastric outlet dysfunction, splenic and portal vein thrombosis, ischemic colitis, colonic necrosis, enteric fistulas, hemorrhages.

- **Systemic complications**: exacerbation of preexisting comorbidities, such as chronic obstructive pulmonary disease, coronary artery disease or chronic liver disease.

- **Organ failure** is defined using the modified Marshall scoring system, that has the advantage of being simple, universally applicable, objective and easily repeatable daily. In AP three organ systems have to be assessed: respiratory, cardiovascular and renal. Respiratory failure is defined with a PaO_2/FiO_2 ratio <300, cardiovascular failure with a systolic blood pressure <90 mmHg non responsive to fluid administration and renal failure with a serum creatinine level ≥1.9 mg/dl (**Table 2**) [7, 9]. If organ failure affects more than one organ system, it is termed multiple organ failure (MOF).

- **Transient organ failure** is defined as organ failure existing for less than 48 hours, while **persistent organ failure** is organ failure persisting for more than 48 hours [7].

There are three degrees of severity of AP:

- **Mild AP**: absence of organ failure and absence of local or systemic complications

- **Moderately severe AP**: presence of transient organ failure (<48 hours) and/or presence of local or systemic complications (in absence of persistent organ failure)

- **Severe AP**: presence of persistent organ failure (>48 hours), that can involve single or multiple organs [7].

Usually, mild AP account for 80–85% of cases, while severe AP is reported in 15–30% of patients [6].

2.5.3 Phases of acute pancreatitis

AP is a dynamic disease with variable scenarios of evolution, but it has two overlapping phases that need to be considered separately to better understand the progression and consequences of this disease.

Organ system	Parameter	Score				
		0	1	2	3	4
Respiratory	PaO_2/FiO_2	>400	301–400	201–300	101–200	≤101
Cardiovascular	Systolic blood pressure (mmHg)	>90	<90, fluid responsive	<90, fluid unresponsive	<90, pH < 7.3	<90, pH < 7.2
Renal	Serum Creatinine (mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9

Table 2.
Modified Marshall scoring system for definition of organ failure in acute pancreatitis. A score of two or more in any system defines the presence of organ failure.

Heart rate	**>90 beats/minute**
Core temperature	<36°C or >38°C
White blood cells count	<4000 cells/mm or >12000 cells/mm³
Respiratory rate	>20 breaths/minute
$PaCO_2$	<32 mmHg

Table 3.
SIRS diagnostic criteria. The presence of two or more criteria defines the presence of SIRS.

The **early phase** usually takes place in the first and second weeks of the disease. It is characterized by the host response to local pancreatic injury and inflammation, with activation of the cytokine cascades that can lead to SIRS (**Table 3**).

In this phase the scenario of AP is still evolving and local complications may be recognized but they are mutable and inaccurate to determine the grade of severity. Furthermore, the morphologic changes due to local complications are not correlated to the extension of organ damage and the severity of organ failure [7].

Instead, the presence of SIRS and his persistence over time are known to be correlated to an increased risk of developing organ failure, are associated to high mortality and are established as early indicator of the likely severity of AP [2, 10, 11]. Persistent SIRS (>48 hours) is associated with a mortality rate of 25% compared with 8% of transient SIRS [3].

Consequently, the determinant of severity in the early phase of AP is the presence and duration of organ failure, that is assessed thorough clinical criteria [7] (see Section 2.6.1 Initial Assessment, **Table 4**) and appears to be related to the development and persistence of SIRS [6].

In this phase, death occurs as a result of the development, the persistence and the progressive nature of organ dysfunction; the reversal of early organ failure has been shown to be important in preventing morbidity and mortality in patient with AP.

Patient characteristic	Age > 55 years	
	Obesity (BMI > 30 kg/m^2)	
	Altered mental status	
	Comorbid disease	
Presence of SIRS	(see **Table 3**)	
Laboratory findings	BUN > 20 mg/dl or rising	*Signs of hypovolemia*
	HCT > 44% or rising	
	Elevated creatinine	
Radiology findings	Pleural effusion	
	Pulmonary infiltrates	
	Multiple or extensive extra pancreatic collections	

BMI, body mass index; BUN, blood urea nitrogen; HCT, hematocrit.

Table 4.
Intrinsic patient-related risk factors for the development of severe disease.

Therefore, if SIRS is identified in this phase of the disease, patients must be treated according to the treatment of a severe AP [6].

The **late phase** usually develops after the second week of the disease and can extent from weeks to months; it is delineated by the persistence of systemic signs of inflammation or by the presence of local complications. Consequently, this scenario develops only in patients with moderately severe or severe AP.

In this phase the disease is still evolving and local complications need to be assessed and characterized with radiological imaging because they may need a specific management. Therefore, although the main determinant of severity in this phase is the persistence of organ failure, the need of radiological definition of local complications requires both clinical and morphological criteria [7].

In the natural history of AP, half of all deaths occur in the first 2 weeks and are mainly due to failure of multiple organ systems while the other half occur after 2 weeks and are mainly due to pancreatic and extrapancreatic infections [5].

2.5.4 Prediction of severity

The three severity degrees of AP have distinct characterizations that have direct implications for clinical management and are associated with different outcome and mortality:

- **Mild AP**: self-limited disease that occurs in approximately 80–85% of patients [5]. By 48 hours after the admission, these patients typically would have substantially improved [6]. Radiological imaging is routinely not mandatory and discharge generally occurs during the early phase. Mortality is rare (<2%) [5, 7].

- **Moderately severe AP**: usually radiological imaging is required to assess the presence and extent of local complications, that may resolve without the need of intervention but that may request prolonged specialist support and care. Mortality is low (<5%) [5, 7].

- **Severe AP**: specific and aggressive treatment and specialist support and care are needed. Mortality is high, ranging from 36% to 50%, and reflects the presence and persistence of SIRS and the development of single or MOF [7, 11].

Persistent SIRS (more than 48 hours) is related to a mortality rate of 25.4% and persistent MOF is associated with a mortality reported to be as great as 42% [10]. Infection of the pancreatic and peripancreatic necrosis occurs in about 20–40% of patients and is associated with worsening organ dysfunctions [2].

Therefore, there are important reasons to define and stratify the severity of AP: the correlation between grade of severity and outcome and mortality, the need to identify patients with potentially severe AP that require aggressive early treatment, the need to identify patients that need transfer from a secondary care center to a specialist one or to intensive care unit, the need to stratify patients into subgroups based on the presence of organ failure and local or system complications to enable patient-tailored treatment that may require a variety of interventions.

Consistently with the definitions of the degrees of severity, the real severity of AP cannot be assessed on admission to the hospital or on first observation because it is not known whether the patient will have transient or persistent organ failure.

Moreover, the evolutions and changes of morphological features of local and systemic complications over time ensure that it is generally not necessary to perform radiological imaging during the first week of admission. When necessary, a CT scan performed 5–7 day after the admission is more reliable in establishing the presence and extent of local complications.

For all these reasons, the dynamic and evolving scenario that characterizes AP need to be reassessed on a daily bases in the early phase of the disease and convenient time points to re-evaluate the patients are usually 24 hours, 48 hours and 7 days after admission to the hospital [7].

Different predictors of severity of AP have been developed over time to improve clinical judgment, including single serum markers and scoring systems incorporating clinical, radiological and laboratory findings. The features of the best predictive criteria are: simplicity, universal applicability across international centers, ability to stratify disease severity easily and objectively, possibility for use at presentation and daily repetition.

Serum lipase or amylase levels are central to diagnosis of AP, but their degree on bloodstream and their decrease have no prognostic value [5, 7].

Many authors consider an acute-phase reactant, the **C-reactive protein** (CRP), as the "gold standard" for disease severity assessment. An elevated CRP concentration of greater than 150 mg/l indicates that AP will have a complicated course with a sensitivity of 85% in the first 72 hours after the onset of symptoms. The major drawback of CRP is that peak levels are reached only after 48–72 hours from the onset of symptoms and therefore is a predictor of severity that takes 72 hours to become accurate. Furthermore, CRP is not disease-specific and can be elevated in other inflammatory conditions [2, 12].

Procalcitonin (PCT) is another acute-phase protein considered as a valuable marker for the detection of severe pancreatitis, with a cut-off value of 0.5 ng/ml. An increased PCT concentration in AP should be observed since the onset of the disease and therefore it is useful in the early prediction of severe AP; nevertheless, some authors suggest that it is more beneficial to measure the PCT level within 24–36 hours from the occurrence of symptoms [13, 14]. A PCT value of 3.8 ng/ml or higher within 96 hours after the onset of symptoms indicated a pancreatic necrosis with a sensitivity and specificity of 93% and 79%. Moreover, an elevated PCT predicts infected necrosis in patients with confirmed pancreatic necrosis and has the ability to indicate a status of bacterial infection [2, 12–14].

Several scoring systems have been developed over time: Ranson score (1974) [15], Glasgow-Imrie score (1978) [16], Acute Physiology and Chronic Health Evaluation II (APACHE-II) (1983) [17], APACHE combined with scoring for obesity (APACHE-O), Simplified Acute Physiology Score (SAPS II) (1984) [18], CT Severity Index (CTSI) (1990) [19, 20], Bedside Index for Severity in Acute Pancreatitis (BISAP) (2008) [21], Harmless Acute Pancreatitis Score (HAPS) (2009) [22], Sequential Organ Failure Assessment (SOFA) (2013) [23], Japanese Severity Score (JPN) (2013 revision) [24].

Ranson score is moderately accurate in stratifying patients in terms of severity but required full 48 hours to be completed, with eleven criteria to be valuated (in additions, some data are not routinely ordered during hospitalization) [15, 25]. **APACHE-II** is very complex: it evaluates the chronic health score and 12 physiologic measurement, is not designed for day to day evaluation and is not specific for AP [2, 17, 25]. **CTSI** is based on local complications showed on CT scan findings and has the drawback of not reflecting the systemic inflammatory response [19, 20, 25]. **BISAP** is one of the most accurate, is very simple (only five criteria), applicable in every day clinical practice and easily applied in the early phases [2, 21, 25].

The International Association of Pancreatology (IAP) and the American Pancreatic Association (APA) evidence-based guidelines for the management of AP, advised the use of **SIRS** to predict severe acute pancreatitis (SAP) on admission and at 48 hours. SIRS can be diagnosed on the basis of four routine clinical measurement (**Table 3**) and persistent SIRS (>48 hours) is associated with MOF and mortality (25% compared with 8% of transient SIRS). Arguments to recommend SIRS over the other predictive scoring systems are widespread familiarity, simplicity and the possibility for repetitive measurements; none of the other scoring systems are considered clearly superior or inferior to (persistent) SIRS [3].

Evidence on the predictive performance of all these scoring systems is variable and their sensitivity and specificity for predicting severe AP range between 55% and 90%, depending on the cut-off value and the timing of scoring. Limitations of these scoring systems have been either the inability to obtain a complete score until at least 48 hours into the illness (missing a potentially valuable early therapeutic window) or the complexity of the scoring system itself [2, 12].

For all these reasons, there are no "gold standard" prognostic scores for predicting severe AP [2]. They are still useful to prove or exclude severe disease but they cannot replace ongoing evaluation by an experienced clinician and a good clinical judgment.

2.6 Management

2.6.1 Initial assessment

Severity score systems are complex, cumbersome and typically require 48 hours to become accurate.

In absence of any available test to determine severity, clinicians need to be aware of clinical finding associated with a severe course. These includes patient's age, comorbid health problems, body mass index, presence of SIRS, signs of hypovolemia (such as elevated blood urea nitrogen (BUN) or elevated hematocrit) and presence of pleural effusion (**Table 4**). These intrinsic patient-related risk factors for the development of severe disease should be used for initial risk assessment and to consequentially provide adequate initial management to patients presenting with AP [6].

2.6.2 Initial management

An adequate initial management should be provided to all patients presenting with AP and patients with organ failure and/or SIRS should be admitted to an intensive care unit whenever possible.

Initial management includes fluid resuscitation with early aggressive hydration, pain management and adequate nutrition. Routine use of prophylactic antibiotics in patients with severe AP and/or sterile necrosis is not recommended.

Early aggressive fluid administration, defined as 250–500 ml/hour of isotonic crystalloid solution, is an effective intervention that is most beneficial during the first 12–24 hours and should be provided to all patients (unless cardiovascular, renal or other related comorbidities preclude it, as the main risk is fluid overload). It amounts to a total infusion of 2500–4000 ml within the first 24 hours and it seems to be sufficient to reach the resuscitation goals within these first hours [2, 3, 5, 6]. Fluid requirement should be reassessed at frequent intervals within 6 hours of admission and for the next 24–48 hours [6]. The response to fluid resuscitation should be based on clinical monitoring of fluid status (heart rate < 120 beats/minute, mean arterial

pressure between 65 and 85 mmHg, urinary output >0.5–1 ml/kg/hour) [3, 5] and on biochemical targets (such as decreasing BUN and hematocrit and maintaining normal creatinine) [5, 6].

Pain is the cardinal symptom of AP and its relief is a clinical priority. All patients must receive analgesia and there is no evidence about any restriction in pain medications: the best recommendations is to adhere to the most current acute pain management guidelines, in a multimodal approach including non-steroidal anti-inflammation drugs (NSAID), opioids, epidural analgesia and patient-controlled analgesia (PCA) [2].

In patients with mild AP there is no need for complete resolution of pain or normalization of pancreatic enzyme levels before oral **feeding** is started. A low-fat soft or solid diet is safe and can be started soon after admission in the absence of nausea, vomiting, severe abdominal pain and ileus [5, 6]. Need for nutritional support may be predicted in severe AP or over day 5 from admission if the symptoms continue to be severe or there is inability to oral feedings [5]. When artificial feeding is required, enteral nutrition should be the preferred treatment and it is recommended to prevent infectious complications. Nasogastric or nasoduodenal feeding are clinically equivalent. Total parenteral nutrition should be avoided and reserved for the cases in which the enteral route is not available, not tolerated or nutritional goals are not met [2, 6].

Infectious complications (both pancreatic and extrapancreatic) are a major cause of morbidity and mortality in patients with AP. Furthermore, patients with infected pancreatic necrosis have a higher mortality rate when compared with patients with sterile necrosis.

Although it was previously believed that preventing the development of infected necrosis was important, different trials have shown no benefit of prophylaxis with antibiotic therapy [5]. Now is established that the role of antibiotics is to treat confirmed infected necrosis instead of prevent infectious complications in patients with sterile necrosis. Antibiotics known to penetrate pancreatic necrosis are carbapenems (such as imipenem), quinolones, fluoroquinolones, clindamycin, piperacillin and metronidazole and their administration may be useful in delaying or avoiding intervention.

Consequently, routine use of prophylactic antibiotics in patients with any type of AP is not recommended unless infection is suspected or confirmed. Furthermore, routine use of antifungal agents, along with antibiotics, is not recommended. Nevertheless, antibiotics should be given for extrapancreatic infections such as cholangitis, catheter-acquired infections, bacteremia, urinary tract infections and pneumonia [2, 3, 6, 26].

There is no current available **pharmacologic therapy** to mitigate AP and current treatment is largely supportive. Considering that pancreatic injury is mediated by autodigestive enzymes, anti-secretory agents such as glucagon and somatostatin have been tested as potential therapies with limited results. Use of protease inhibitors agents (such as gabexate mesilate) have been studied with the aim of blocking intrapancreatic activation of digestive enzymes but several trials showed conflicting results on clinical benefit. Also administration of indomethacin and steroid therapy have been assessed in clinical trials but their role remains to be determined [27]. A recent Cochrane review about pharmacological intervention for AP stated that there was no evidence of difference in short-term mortality between the groups in any of the comparisons. Despite this evidence, the authors underlined that interventions with at least two clinical benefits were: octreotide (somatostatin analog), which was

associated with fewer serious adverse events and a lower proportion of people with organ failure; and gabexate mesilate, which was associated with fewer adverse events and a lower proportion of people requiring an additional invasive intervention compared to inactive intervention [28].

2.6.3 Patient-tailored management (of late phase of acute pancreatitis)

Whether AP progresses to the late phase of the disease, patients may require a variety of interventions that go beyond the initial management. Patient-tailored management may include ERCP, endoscopic ultrasonography (EUS), endoscopic and/or radiological drainage or surgical intervention for treatment of local complications and referral for cholecystectomy to prevent recurrent attacks and potential biliary sepsis [6].

ERCP is indicated in patients with biliary pancreatitis with common bile duct obstruction and/or cholangitis [3, 5].

Asymptomatic acute peripancreatic fluid collections and asymptomatic pseudocysts do not require therapy. The development of infection in the necrotic collection is the main indicator for therapy and treatment should be delayed preferably for more than 4 weeks [3, 5, 6]. Clinical and imaging signs are accurate and routine percutaneous fine needle aspiration and culture is not required [3, 5].

The optimal intervention strategy is always a step-up approach: initial broad-spectrum antibiotics administration, subsequent percutaneous radiological interventions followed, if needed, by endoscopic transmural drainage or endoscopic debridement and eventually by surgical approach [3, 5, 6]. Minimally invasive operative methods of necrosectomy and minimally invasive surgical approaches are always preferred to open necrosectomy [6]. The optimal strategy must be individualized for every patient and should be discussed by a multidisciplinary group of experts.

To prevent recurrence of AP, cholecystectomy should be performed before discharge in patient with mild gallstone AP. In this subgroup of patients, cholecystectomy performed 25–30 days after discharge has a higher rate of complications as compared with cholecystectomy performed during the initial hospitalization and a delay of cholecystectomy for more than a few weeks is associated with a high risk of relapse (up to 30%) of AP. Instead, in patient with necrotizing biliary AP, cholecystectomy should be delayed until active inflammation and fluid collections resolve or stabilize [3, 6]. In AP without biliary etiology, other protective measures to prevent relapses are mandatory such as smoking cessation, abstinence of alcohol intake, withdraw of implicated medications and tight control of hyperlipidemia.

2.7 Long-term consequences

Approximately 20–30% of patients develop pancreatic exocrine and endocrine dysfunction after AP and 30–50% of those patients will evolve in CP. Risk factors for these long-term consequences are the etiology, the severity and the degree of pancreatic necrosis of the initial attack of AP [5].

3. Chronic pancreatitis

CP is a clinical entity resulting from progressive inflammation and irreversible fibrosis of the pancreas due to cumulative damage to the pancreas over time.

It is a disease with various manifestations that can severely affect quality of life, while its long-term complications such as exocrine pancreatic insufficiency (EPI), diabetes mellitus, and risk of pancreatic cancer can become life-threatening. Diagnosis of CP can be challenging because, despite recent advances in imaging technology, radiologic findings are not apparent until late stages of the disease.

Only dynamic observation of patients with controlled follow-up allows us to classify pancreatitis and better define the disease by assigning definitive labels supported by biochemical and radiological sources that are well characterized by the various classification systems available. The clinician should recognize pancreatitis at an early stage but avoid making a "definitive" classification immediately.

3.1 Definition

In the last decade, advances in clinical and translational sciences have redefined our understanding of CP, thus changing the definition, the diagnosis and the management of the disease.

The traditional clinopathologic-based definition described CP as a "*a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function*". Such a diagnostic assessment resulted in a delay between symptom onset and diagnosis, failing to identify the underlying etiology, without predicting the clinical course or guide preventative treatments, being limited to symptomatic or supportive care and replacement of lost gland function [29].

In 2016, a new Mechanistic Definition of CP was published and adopted worldwide. This definition affirmed the characteristics of end-stage disease (**Table 5**) and addressed the disease mechanism as "*a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress*". The new paradigm is to focus on diagnosing the mechanistic disorder underlying the pathogenic process early in the disease course and managing the syndrome to change the natural course and to minimize adverse disease effects. Within this framework it is important to recognize the difference between pancreatic dysfunction, pancreatitis-related disorders, and pancreatic disease [30, 31].

Pancreatic atrophy
Fibrosis
Pain syndromes
Duct distortion and strictures
Calcifications
Pancreatic exocrine dysfunction
Pancreatic endocrine dysfunction
Dysplasia

Table 5.
Characteristics of end-stage chronic pancreatitis.

3.2 Epidemiology

The epidemiology of CP is poor compared with other illnesses. There are few studies that look at the population distribution of CP, and it is important to note that these data are not available from large parts of the world. This is likely related to the difficulties in conducting such studies due to the low prevalence of the disease, the establishment of an accurate diagnosis, and the focus of previous studies on describing the clinical profile and natural history of the disease. Over the past two decades, there has been an interest in documenting the distribution of pancreatic disease in the population. Incidence of CP is currently estimated between 4.4 and 14 per 100,000 people, with a prevalence of 36.9–52.4 per 100,000 persons, and a male predominance by a factor of 1.5–4.6 [32, 33]

In 2016, a systematic review by Xiao et al. [34], that included only high-quality studies conducted on general populations, demonstrated a global pooled incidence of CP of 10 cases per 100,000 general population per year.

A recent 25-year population-based Danish study by Olesen et al. evaluated the incidence and the prevalence of CP between 1994 and 2018. The mean incidence rate was 12.6 per 100,000 person years for the total population; 8.6 vs. 16.7 per 100,000 person years in women and men, respectively. The Authors demonstrated that over a 25-year observation period the prevalence of CP was increasing in the Danish population (from 126.6 in 1996 to 153.9 in 2016), while the incidence remained stable; the mean age at CP diagnosis increased by almost a decade (52.1–60.0 years) [35].

3.3 Etiology

3.3.1 Risk factors

The most common risk factor for CP is alcohol abuse [36, 37]. In 1995, a study from Levy et al. demonstrated a logarithmic relationship between the relative risk of developing CP and the quantity of consumed alcohol, although the type of alcohol consumed is irrelevant [38]. There is not a threshold value, but a minimum of 80 g alcohol per day for a period of at least 6 years is considered to be a risk factor for the development of CP. An average of 18 ± 11 years elapses between the start of excessive alcohol consumption and the development of pancreatitis [39, 40].

Smoking is an independent risk factor. It accelerates the progression of CP, even with alcohol abstinence. It leads to pancreatic pain exacerbations and to calcifications. All patients should be advised to quit smoking [41–43]. In 2009, Yadav et al. published the results of the North American Pancreatitis Study 2 that prospectively enrolled 540 patients with CP. A dose-dependent association between smoking and CP was demonstrated; and patients without an history of alcohol but with 21–35 pack years have an increased risk of CP with a 3.26 odds ratio [44].

Primary hyperparathyroidism (pHPT) can lead to CP, with or without calcifications. 1% of patients with CP suffers from pHPT, conversely 12% of patients with pHPT also have pancreatitis, thus leading to a 28-fold increased risk of developing pancreatitis in this cohort of patients [45, 46].

Whether the anatomic anomaly pancreas divisum (the most common congenital malformation of the pancreas) is a risk factor for the development of CP is still a matter of debate. The S3-consensus conference on CP have reached an agreement on the following statement: “the presence of pancreas divisum without any further risk factors tend not to lead to chronic pancreatitis” [47].

Several genes have been associated with the diagnosis of CP. Genetic testing aim is to provide early information about the etiology of disease-related disorders that are contributing to the pathogenic process, to assist in decision making, and to help prevent the development of irreversible CP [48].

The most important genetic risk factors are variants in cationic trypsinogen (PRSS1), SPINK1 and carboxypeptidase A1 (CPA1). Further genetic susceptibility genes are CFTR, chymotrypsinogen C (CTRC) and carboxyesterlipase (CEL) [49–54].

Trypsinogen is a key molecule in the pathogenesis of pancreatitis, up to 66% of patients with hereditary pancreatitis have a mutation of the PRSS1 gene. Such mutations lead to CP with a penetrance of up to 80% and an autosomal dominant inheritance pattern [55–58].

Mutations of the SPINK1 gene predispose to idiopathic CP, occurring in as many as 30% of patients, however only in 1–2% of the general population. The N34S mutation in the gene encoding SPINK1 bears an odds ratio of 11.0 in developing CP.

Cystic fibrosis is an autosomal recessive disease with an estimated incidence of 1:2500. The first description of an association between CFTR variants and CP was published in 1998 [59]. The association between gene mutations and CP has an odds ratio of around 3–5 [55, 60]. CP patients carrying CFTR variants harbor at least one mild variant allele giving them residual CFTR function. Pancreas involvement may vary from a complete loss of exocrine and endocrine function to almost normal function. Molecular changes in the CFTR gene are associated to up to 30% of patients with idiopathic pancreatitis.

Patients with a CTRC mutation have an increased risk of developing CP. The first report dates back to 2008 [52]. Such mutations occur in 3.3% of patients with idiopathic pancreatitis.

In addition to those etiologic factors, autoimmune pancreatitis has been recently characterized. First reported in 1961 by Sarles [61], Yoshida first postulated this clinical entity in 1995 [62]. This is a systemic fibroinflammatory disease in which the pancreas is one of the affected organs. Men are affected twice than women. Clinical symptoms include abdominal pain, jaundice and recurrent episodes of pancreatitis. Radiological findings include “sausage-shaped pancreas” and diffuse or segmental Wirsung stenosis, often without prestenotic dilation. Serum levels of immunoglobulin (Ig) G and IgG4 have been found increased in the Asian patients, but only in 50% of European ones. Diagnosis is reached according to the HiSORT criteria (**Table 6**) [63] which include histology, serology, other organ involvement and response to steroid therapy [64–66].

3.3.2 Classification models

Distinct classification systems have been developed but, so far, no globally accepted classification system has been established. Classification systems currently in use are: Manchester classification; ABC classification; M-ANNHEIM; TIGAR-O; and Rosemont classification. Only the Toxic/metabolic, Idiopathic, Genetic, Autoimmune, Recurrent acute pancreatitis, and Obstructive (TIGAR-O) and the pancreatitis with Multiple risk factors-Alcohol consumption, Nicotine consumption, Nutritional factors, Hereditary factors, Efferent duct factors, Immunological factors, Miscellaneous and rare metabolic factors (M-ANNHEIM) classification systems take the etiology of CP into account.

The M-ANNHEIM system is a multirisk factor classification system. It adds information on disease activity and stage, evaluating the role of various risk factors on the

Category	Criteria
Histology	One of the following: 1. Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis (LPSP) 2. Lymphoplasmacytic infiltrate with storiform fibrosis showing abundant IgG4 positive cells (≥10 cells/HPF)
Imaging CT/MRI	Typical: diffusely enlarged gland with diffuse rim enhancement, diffusely irregular attenuated pancreatic duct Other: focal pancreatic mass or enlargement; focal pancreatic duct stricture; pancreatic duct stricture, pancreatic atrophy; pancreatic calcification or pancreatitis
Serology	Elevated serum IgG4 level (>135 mg/dl)
Other organ involvement	Hilar/intrahepatic biliary strictures, persistent distal biliary strictures, parotid or lacrimal gland involvement, mediastinal lymphadenopathy or retroperitoneal fibrosis
Response to steroid therapy	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy

LPSP, lymphoplasmacytic sclerosing pancreatitis; CT, computed tomography; MRI, magnetic resonance imaging; IgG4, immunoglobulin G4; HPF, high powered field.

Table 6.
The Mayo clinic HiSORT criteria for the diagnosis of AIP.

course of CP [67]. Relying upon traditional clinicopathologic criteria, and resulting in a score between 0–25, it provides diagnostic criteria for etiology, clinical and diagnostic stage (**Table 7**).

The TIGAR-O classification system comprises six etiologic groups: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent AP, and obstructive groups. It

Clinical feature	Points
Patient report of pain	
No pain without therapy	0
Recurrent acute pancreatitis (RAP)	1
No pain with therapy	2
Intermittent pain	3
Continuous pain	4
Pain control	
No medication	0
Use of nonopioid drugs or use of mild opioids (WHO step 1 or 2)	1
Use of potent opioids (WHO step 3) or endoscopic intervention	2
Surgical intervention	
Pancreatic surgical intervention for any reason	4
Exocrine insufficiency	
Absence of exocrine insufficiency	0
Presence of mild, moderate, or unproven exocrine insufficiency not requiring enzyme supplementation (including patient reports of intermittent diarrhea)	1
Presence of proven exocrine insufficiency (according to exocrine function tests) or presence of marked exocrine insufficiency defined as steatorrhea (>7 g fat/24 hour), normalized or markedly reduced by enzyme supplementation	2

Clinical feature	Points
Endocrine insufficiency	
Absence of diabetes mellitus	0
Presence of diabetes mellitus	4
Morphologic status on pancreatic imaging (according to Cambridge classification)	
Normal	0
Equivocal	1
Mild	2
Moderate	3
Marked	4
Severe organ complications	
Absence of complications	0
Presence of possibly reversible complications	2
Presence of irreversible complications	4

Table 7.
The M-ANNHEIM scoring system for the grading of clinical features of chronic pancreatitis.

has been validated in multiple international studies, and in 2019 it was revised to include new insights from the past 20 years. It is designed as a hierarchical checklist to quickly document and track specific factors that may contribute to progressive pancreatic disease (**Table 8**) [68].

Toxic-metabolic
Alcohol-related (susceptibility and/or progression)
3–4 drinks/day
5 or more drinks/day
Smoking (if yes, record pack-years)
Non-smoker (<100 cigarettes in lifetime)
Past smoker
Current smoker
Other, NOS
Hypercalcemia (total calcium levels >12.0 mg/dl or 3 mmol/l)
Hypertriglyceridemia
Hypertriglyceridemic risk (fasting > 300 mg/dl; non-fasting > 500 mg/dl)
Hypertriglyceridemic acute pancreatitis, history of (>500 mg/dl in first 72 hours)
Medications (name)
Toxins, other
Chronic kidney disease (CKD)—(CKD Stage 5: end-stage renal disease, ESRD)
Other, NOS
Metabolic, other
Diabetes Mellitus (with the date of diagnosis if available)
Other, NOS
Idiopathic
Early onset (<35 years of age)
Late onset (>35 years of age)
Genetic
Suspected; no or limited genotyping available
Autosomal dominant (Mendelian inheritance—single gene syndrome)
PRSS1mutations (hereditary pancreatitis)
Autosomal recessive (Mendelian inheritance—single gene syndrome)

CFTR, 2 severe variants in *trans* (cystic fibrosis)
CFTR, <2 severe variants in *trans* (CFTR-RD)
SPINK1,2 pathogenic variants in *trans* (SPINK1-associated familial pancreatitis)
Complex genetics (non-Mendelian, complex genotypes ± environment)
Modifier genes (list pathogenic genetic variants)
PRSS1-PRSS1 locus
CLDN2 locus
Others
Hypertriglyceridemia (list pathogenic genetic variants)
Other, NOS
AIP/steroid responsive pancreatitis
AIP Type 1—IgG4-related disease
AIP Type 2
RAP and SAP
Acute pancreatitis (single episode, including date of event if available)
AP etiology—extra-pancreatic (excluding alcoholic, HTG, hypercalcemia, genetic)
Biliary pancreatitis
Post-ERCP
Traumatic
Undetermined or NOS
RAP (number of episodes, frequency, and dates of events if available)
Obstructive
Pancreas divisum
Ampullary stenosis
Main duct pancreatic stones
Widespread pancreatic calcifications
Main pancreatic duct strictures
Localized mass causing duct obstruction

Table 8.
The TIGAR-O Version 2.0 risk/etiology classification, short form.

3.4 Diagnosis

The diagnosis is made using a combination of modalities, including exposure risk, underlying predisposition, cross-sectional imaging, and direct and/or indirect pancreatic function tests. The first step to diagnose CP is to perform a detailed history to attempt to elucidate underlying risk factors. Key elements that must be investigated are hypertriglyceridemia, autoimmune diseases, diabetes mellitus, and prior AP episodes [68, 69]. The most common clinical manifestations of CP are abdominal pain and steatorrhea depending on the degree of pancreatic dysfunction.

Pain is the dominant symptom of CP. It is usually recurrent and can be either episodic (type A) or persistent (type B). Up to 80–90% of patients complain of pain during the course of the disease. Painless pancreatitis occurs in 10–20% of patients [40, 70–73].

The occurrence, the etiology and the sequalae of prior episodes of AP should be determined. Family history is informative especially in patients with early-onset disease to determine if hereditary or genetic causes are responsible. The use of voluptuous substances such as tobacco and alcohol should be investigated as these are the main driving factors, for example using the AUDIT questionnaire.

Laboratory values should be tested: triglyceride-levels; Ca^{++}-levels for ruling out elevated pHPT; carbohydrate deficient transferrin (CDT)/phosphatidylethanol levels.

The sensitivity of pancreatic function testing to diagnose CP is low. To date, there are no randomized clinical trials, systematic reviews or meta-analysis which specifically address the use of pancreatic function tests to diagnose CP. As such, pancreatic function tests should only be used as ancillary test in making the diagnosis [74–76].

Pancreas has a large reserve and only a significant loss of function (usually >90%) results in the clinically apparent symptoms of vitamin deficiency, steatorrhea and azotorrhea [77]. EPI is the result of the imbalance within nutritional intake, pancreatic digestive enzyme delivery to the small intestine, intestinal adaptation to disease and nutritional needs. CP is an evolving process, and exocrine function is progressively impaired from a reduced functional capacity to exocrine failure in the late phase. To detect mild or moderate exocrine pancreatic impairment, invasive tests employing a hormonal secretagogue (CCK or secretin stimulation tests) maximally stimulating pancreatic secretion can be useful. Such tests are sensitive but poorly specific, they are not diagnostic [78, 79]. Conversely, nonhormonal tests of pancreatic function can detect severe exocrine insufficiency only. Indeed, fecal elastase and fecal chymotrypsin can be used in the follow-up of selected patients for identifying a progressive impairment in pancreatic function by which the chronicity of the inflammatory process can be confirmed [80–82].

It is critical to demonstrate typical morphological changes in the pancreas, as imaging is a surrogate for histology. Diagnosis is established via high quality imaging modalities, which allow identification of the following signs: increased density of the parenchyma, atrophy of the gland, calcification, pseudocysts and irregularities of the main pancreatic duct and its side branches. Diagnosis should be based on imaging performed in symptomatic patients presenting with indicators suggestive of pancreatic disease [29].

MR with MR cholangio-pancreatography and dynamic MRCP following secretin administration and endoscopic ultrasound are the imaging techniques of choice to diagnose early CP and to identify pancreatic malformations in patients with CP. In early CP dynamic MRCP during secretin administration is useful in identifying initial morphological changes of the pancreatic duct system and specifically of the side branches [83].

CT is the technique of choice in diagnosing and localizing pancreatic stones inside the lumen of the main pancreatic duct or side branches, and in patients with CP and flare of the disease [84].

Transabdominal ultrasonography (US) is not able to identify early CP, but can confirm the diagnosis of advanced CP, since it identifies the thinning of the pancreatic parenchyma, the irregularity of the pancreatic margins, dilatation of the main pancreatic duct and of the side branches, and endoductal calcified stones [85].

When the diagnosis cannot be made by radiological or EUS morphologic criteria and clinical and functional evidence of CP is strong, histological examination via EUS-guided fine-needle biopsy is the gold-standard to diagnose CP [36].

Testing for germline mutations is not diagnostic of CP, but it rather identifies a population at risk improving the accuracy of biomarkers and identifies the mechanism underlying the pathogenic process. Therapies can target the mechanism, and knowing the mechanism allow to select the most appropriate drug. Patients should be referred to a genetic counselor for evaluation. At minimum patients with idiopathic CP should be evaluated for PRSS1, SPINK1, CFTR, and CTRC gene mutation analysis.

3.5 Management

3.5.1 Pain

Abdominal pain is the most common complication and prevailing symptom of CP. It can manifest through a spectrum of intensity, form mild and intermittent to severe unrelenting. Pain is experienced by 75% of patients at the time of presentation and up to 97% during the clinical course. The pathophysiology is multifactorial and results from pancreatic and extra-pancreatic causes. Pancreas-related causes include: parenchymal and nerve sheaths inflammatory infiltrates, augmented pressure by obstruction flow of pancreatic juice and increased pancreatic capsule tension due to raised pancreatic parenchymal pressure. Extra-pancreatic causes include gastric or duodenal ulcers and meteorism caused by bacterial overgrowth and maldigestion [47, 86].

The NAPS-2 Study categorized five distinct pain patterns according to severity and pain control (**Table 9**) [87].

The only pain score explicitly validated for assessing pain in patients with CP has been published in 1995 by Bloechle et al. [88]: the visual analogue scale. Pain management should follow the WHO three-step analgesic ladder. However, WHO pain management has not been consistently used in the available literature, thus the question about its effectiveness cannot be answered.

The natural course of pain in CP is characterized by a variable percentage of patients (47–80%) achieving spontaneous pain relief from 10 to 15 years from onset. However, a part of patients will suffer of pain indefinitely. Waiting for a spontaneous pain relief has been defined not reliable by the American Gastroenterological Association (AGA) [36].

Endoscopic treatment (ET) is recommended as a first-choice therapy in patients with an obstructive type of pancreatic pain and in patients with a pancreatic duct dilatation. This could, also, be useful as a bridge to surgery. The aim of ET is decompression of an obstructed main pancreatic duct, it decreases the numbers of hospitalizations for pancreatic pain and reduces analgesics intake. Extracorporeal shock wave lithotripsy (ESWL) therapy in painful CP is indicated if the stone size is >5 mm, the stone is located in the head or pancreatic body, and there are no strictures of the main pancreatic duct. It should be combined with ET in cases of large stones with pancreatic duct stricture [36, 47].

Surgical options for pain are classified into three categories: decompression (focusing on ductal hypertension), resection (focusing on inflammatory masses in the pancreatic head), and mixed techniques. Decompression is recommended in patients with a main pancreatic duct >7–8 mm and no inflammatory mass. Pain relief is achieved in 66–91% of patients, however, the long-term results show up to 50%

Pain pattern	Description
A	I have episodes of mild to moderate pain, usually controlled by medicines
B	I have constant mild to moderate pain, usually controlled by medicines
C	I am usually free of abdominal pain, but I have episodes of severe pain
D	I have constant mild pain that is controlled, plus episodes of severe pain
E	I have constant severe pain that does not change

Table 9.
Description of pain patterns used in the NAPS2 study.

recurrences. Resection in patients with an inflammatory mass or an obstructive CP of the body or tail. Pancreaticoduodenectomy is effective in 75% of patients but with a significant morbidity (20%), as such most authors favor the more conservative mixed techniques. Mixed techniques achieve a short-term pain relief in up to 70–100% of patients and a long-term pain relief in 82–100%. Mixed techniques are based on the resection of the inflammatory mass in the pancreatic head and drainage of the obstructed main pancreatic duct (body and tail). The most widely used techniques are the duodenal preservation (Berger) or the Frey method which consists in a longitudinal pancreaticojejunostomy and in the coring out of the pancreatic head [47, 89].

A pain management strategy must be well structured and conducted with a logical approach to minimize long term complication and sequelae. Is recommended to early involve a pain management specialist during the clinical course, as delays lead to poorer health and pain control [90].

3.5.2 Lifestyle

Complete cessation of alcohol and tobacco use is of utmost importance. Patients must be aware that ongoing use will sustain the cycle of pain and lead to further progression of the disease. Cognitive and mindfulness-based therapies should be offered to all patients, especially for those who need assistance with abuse disorder.

3.5.3 Enzyme replacement

A weight loss of more than 10% of the body weight, steatorrhea with a fecal fat excretion of more than 15 g/die (or a pathological pancreatic function test) in combination with clinical signs of malabsorption (dyspeptic symptoms with severe meteorism or diarrhea) are a clinical indication for pancreatic enzyme replacement therapy. Abdominal complaints (diarrhea/steatorrhea, abdominal distension/meteorism and pain) may be due to intestinal motility disorders caused by maldigestion and malabsorption [91]. Enzyme supplements are administered by gastric-acid-protected encapsulated microsphere and contain pancreatin, with the main components being lipase, amylase, trypsin and chymotrypsin. A successful treatment is measured by improvement of the disease symptoms. Therapy with pancreatin purely as a trial for 4–6 weeks may also be beneficial if symptoms are unclear [91–94].

An untreated severe EPI results in a severe malabsorption syndrome that manifests in the form of steatorrhea, deficiency of fat-soluble vitamins, weight loss and finally cachexia [71, 95, 96]. The success of enzyme replacement therapy should be monitored using clinical parameters (weight gain, long-term normalization of the vitamin status, cessation of abdominal symptoms).

3.6 Surveillance

Incidence of pancreatic cancer is increased in long-lasting CP. Several studies have addressed this topic. The paper by Bansal and Sonnenberg in 1995 found a clear relationship between CP and pancreatic cancer (OR 2.23; 95% CI 1.43–3.49) [97].

Should patients with CP be screened for pancreatic cancer? The United States Preventive Task force has stated that screening the general population for pancreatic cancer by current modalities is not recommended.

4. Surgical treatment of complications

Local complications such as pancreatic and/or peripancreatic fluid collections can occur after an episode of AP or after recrudescence of CP or a blunt, penetrating, iatrogenic pancreatic trauma. Peripancreatic fluid collections, with or without a necrotic component, are early manifestations of the pancreatic inflammatory process.

In asymptomatic patients, clinical observation and periodic imaging follow up represent the most successful management. Prognosis and management are greatly affected by the recognition between sterile and infected pancreatic necrosis. In symptomatic patients, with rapidly enlarging pseudocysts or systemic manifestations of organ failure sustained by an infectious process, an interventional treatment is indicated. In this case endoscopic drainage approach is the first choice, especially when fluid collection is close to gastroduodenal lumen. A combination of techniques is possible in patients with large collections, extended in pelvis and paracolic gutters, or multiple collections [98].

Endoscopic management of pseudocysts and walled-off pancreatic necrosis (WOPN) has been described in a dedicated chapter of this Book.

Endoscopic drainage techniques consist in [99]: *transmural or transpapillary drainage*.

Percutaneous drainage remains an important treatment modality for patients with symptomatic collections. It may be used both as primary therapy and as an adjunct to other techniques. According to the last International [3], American [100] and Japanese [24] guidelines, percutaneous catheter (or endoscopic transmural drainage) should be the first step in the treatment of patients with suspected or confirmed (walled-off) infected necrotizing pancreatitis. This is applied to decompress retroperitoneal fluid collections, to provide a rapid and effective means for source control in patients with infected pancreatic necrosis. The positioning can be performed via the transperitoneal or retroperitoneal approaches. Retroperitoneal route is generally preferred because it avoids peritoneal contamination, enteric fistulas and facilitates a possible step-up approach.

The surgical odyssey in managing necrotizing pancreatitis is a notable example of how evidence-based knowledge leads to improvement in patient care. In the beginning of the 20th century surgeons such as Mayo Robson, Mickulicz, and Moynihan, in the context of the progression of anesthesia, were induced to deploy laparotomy in an effort to treat complications of severe AP [101]. Over the next decades surgical intervention became the therapy of choice despite a mortality rate greater than 50%. Extensive pancreatic resection became the treatment of choice in the 1960s and 1970s. Innovations and increased accuracy in radiological techniques led to new approaches for management. Since 1990s several studies proved that nonoperative management of patients with sterile pancreatic necrosis was superior to surgical intervention, and that delayed intervention provided improved surgical mortality rates. The treatment of infected necrosis shifted to a more conservative approach also thanks to a comprehensive knowledge of the physio-pathological process of the systemic inflammatory response and the adoption of novel antibiotics in curbing systemic toxicity and protecting against organ failure.

According to the last guidelines of the Working Group of the IAP/APA published in 2013 [3] and of the AGA published in 2020 [100], a symptomatic sterile pancreatic necrosis is an indication for intervention (either radiological, endoscopical or surgical). In case of infected pancreatic necrosis invasive procedures (e.g. percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed, where possible, until at least 4 weeks after initial presentation to permit the collection to become "walled-off".

Percutaneous drainage, alone or in combination with other minimally invasive approaches, can be an effective means for source control in patients with infected pancreatic necrosis. A significant number of patients (23–47%) will resolve their necrosis with percutaneous drainage alone. In those with persistent disease, a step up to operative intervention may be undertaken. The tract of the drain is utilized to access the retroperitoneal space for an intracavitary videoscopic necrosectomy by which drains are left in the cavity for lavage and fistula control [102–104].

Open debridement with external drainage still plays an important, albeit limited, role. After access to retroperitoneum, fluid is evacuated and necrotic dissection and debridement is made. In biliary pancreatitis, cholecystectomy should be practiced but it is associated with increased incidence of postoperative bile leak or biliary injury. Colon resection and colostomy have to be considered if mesocolon is involved in peripancreatic necrosis. A feeding enteral tube and at least two-four drainage tubes should be placed [105].

Each approach has distinct peculiarities with pros and cons that must be weighted in each case planning: pattern of disease, physiology of the patient, expertise of the multidisciplinary team, and the resources of the center [100].

Conflict of interest

The authors declare no conflict of interest.

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