


## Review Article

# Management of Acute Pancreatitis: Conservative Treatment and Step-Up Invasive Approaches—Evidence-Based Guidance for Clinicians

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Although acute pancreatitis is one of the most common conditions that physicians face in daily practice, different approaches are still being followed. Given that in 20–30% of cases, acute pancreatitis progresses to the severe form with single- or multiorgan failure and is often associated with admission to the intensive care unit, proper management is important. This article is aimed at emphasizing the importance of proper conservative treatment of acute pancreatitis and at focusing on intervention criteria in case of complications, analyzing additionally the step-up endoscopic and surgical approaches. The most common mistakes in conservative treatment include inadequate initial fluid resuscitation, abuse in the administration of antibiotics, insufficient analgesia, avoidance of oral feeding, and inappropriate use of imaging techniques. Moreover, the timing and indications for endoscopic retrograde cholangiopancreatography and cholecystectomy are crucial. Furthermore, in case of unsatisfying response to conservative treatment, which mainly happens during necrotic pancreatitis, early intervention is not indicated and a minimally invasive approach must be adopted firstly, 4 weeks after the onset of the disease, and before any surgical intervention. Each medical procedure has specific indications and must be used in the appropriate occasion. As a result, clinical doctors must be familiar both with the intervention criteria and the indications of each method. The proper management of acute pancreatitis is essential and life-saving. That is valid both for the conservative treatment and for the invasive approaches.

## 1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas and constitutes one of the most common diseases of the gastrointestinal tract [1]. The incidence of AP is 34 per 100,000 people in the general population [1]. It is the cause of significant morbidity, repeated hospitalizations, and considerable expenses in the health system [2]. Furthermore, it may be associated with single- or multiple-organ dysfunctions requiring surveillance into an intensive care

unit (ICU) [1, 2]. The overall mortality rate is estimated to be approximately 20% [1, 2].

Aetiologic factors include gallstones, alcohol intake, trauma, malignancy, metabolic disorders, genetic factors, autoimmunity, drugs, infections, and idiopathic causes [3–12] (Table 1).

The pathogenesis of AP is the subject of ongoing research, which has given prominence to major pathophysiological events. More precisely, studies have revealed mechanisms of calcium-mediated acinar cell injury and death, whereas

TABLE 1: Most common causes of acute pancreatitis.

Causes of acute pancreatitis	References
(i) Gallstones	[3]
(ii) Ethanol	[3]
(iii) Trauma	[3]
(iv) Surgery (aortic surgery, pancreatic surgery)	[3]
(v) Steroids	[10]
(vi) Malignancy (pancreas, biliary duct, gallbladder, liver, stomach, ampulla of Vater, and duodenum)	[3, 5]
(vii) Infections (viral, bacterial, fungal, and parasitic)	[3, 11]
(viii) Genetic factors (PRSS1, SPINK1, CFTR, CASR, CTRC, CLDN2, and CPA1)	[8]
(ix) Autoimmune	[9]
(x) Metabolic disorders (hypertriglyceridemia, hypercalcemia)	[6, 7]
(xi) Postendoscopic procedures (ERCP, EUS)	[4]
(xii) Drugs (furosemide, losartan, and azathioprine)	[10]
(xiii) Scorpion sting	[3]
(xiv) Idiopathic	[12]

ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound.

store-operated calcium entry channels and mitochondrial permeability transition pores have been characterized as key factors for potential apoptosis and necrosis [2, 13]. Further insights have been made into crucial pathogenic cellular events such as endoplasmic reticulum stress, autophagy, and impaired trafficking [2, 13]. New findings elucidated that the intra-acinar trypsinogen activation, which had been hypothesized to be the central mechanism of pancreatitis, causes pancreatic injury, but the inflammatory response in acute pancreatitis develops independently and is provoked by early activation of inflammatory pathways [2, 14, 15].

Although AP is often uncomplicated, there are few complications of the disease that are combined with its moderate and severe forms (Table 2) [16–20]. These complications can be categorized as local and systemic [16–20] (Table 3).

The importance of the proper management of patients with AP is critical [16–20]. Although this condition has been well discussed in the current literature, different approaches are still being followed. There is no consensus for the timing and type of interventions that should be used, whereas the availability of new minimally invasive techniques has modified entirely the therapeutic plan [16, 20]. Moreover, despite the availability of guidelines, recent studies auditing the clinical management of acute pancreatitis have depicted non-compliance in several aspects with the evidence-based guidelines [16, 20]. The purpose of this article is to focus on the importance of proper conservative treatment of acute pancreatitis analyzing the most common mistakes that are made, to summarize intervention criteria and invasive techniques that are used in daily practice for familiarization, and to offer a reliable framework that any clinical doctor should follow in order to treat properly acute pancreatitis.

## 2. Conservative Management

The conservative treatment of AP in its early phase, 24–72 hours from the onset of the disease, is crucial. Proper man-

TABLE 2: Severity of acute pancreatitis.

Severity	Criteria
Mild	(i) No organ failure
	(ii) No complications
	(iii) Typically, resolution in the first week
Moderate	(i) Transient organ failure ( $\leq 48$ hours) or
	(ii) Local/systemic complications without persistent organ failure
Severe	(i) Persistent organ failure ( $> 48$ hours)
References:	[16, 19, 20].

agement can change the entire course of the disease and prevent pancreatic necrosis.

**2.1. Fluid Resuscitation.** Hypovolemia occurs as a result of multiple factors in patients with AP, including vomiting, reduced oral intake, third spacing of fluids, increased respiratory losses, and diaphoresis [16]. In addition, microangiopathic effects and oedema of the pancreas decrease blood flow, leading to increased cellular death and necrosis, while pancreatic enzymes continue to activate cascades of inflammation that increase vascular permeability and third-space loss, and worsen pancreatic perfusion [16, 21].

According to the 2019 World Society of Emergency Surgery (WSES) guidelines, early fluid resuscitation is indicated for patients with AP to prevent hypovolemia and hypoperfusion without waiting for haemodynamic worsening [16]. Based on the pathophysiological mechanisms mentioned above, fluid resuscitation is essential and it seems that early hydration maintains the microcirculation, which prevents pancreatic necrosis [16, 22]. The volume needed to prevent necrosis is unknown, but it seems to be individualized for each patient [22]. The American College of Gastroenterology suggests aggressive early hydration, such as 250–500 ml/hour, especially for the first 24 hours [17]. Age, weight, and cardiac

TABLE 3: Complications of acute pancreatitis.

Local complications	Systemic complications	References
(i) Peripancreatic fluid collections (<4 weeks)	(i) Renal dysfunction	[16–20]
(ii) Necrotic collections (<4 weeks)	(ii) Cardiovascular deterioration	[16–20]
(iii) Pancreatic pseudocysts (>4 weeks)	(iii) Respiratory dysfunction	[16–20]
(iv) Walled-off necrosis (>4 weeks)	(iv) Comorbidity worsening	[16–20]
(v) Infected necrosis	(v) SIRS	[16–20]
(vi) Splenic/portal vein thrombosis		[16, 19, 20]
(vii) Colonic necrosis		[16, 19, 20]
(viii) Gastric outlet syndrome		[16, 19, 20]
(ix) Acute necrotizing cholecystitis		[16, 19, 20]
(x) Abdominal compartment syndrome		[16, 19, 20]
(xi) Bowel fistula		[16, 19, 20]
(xii) Bleeding		[16, 19, 20]

or renal comorbidities should be accounted for to prevent volume overload [16, 17, 22].

The preferable method to determine the volume status and to adjust the fluid administration after the first 24 hours is central venous pressure (CVP) measurement [16, 17, 22]. The intrathoracic blood volume index seems to be more accurate but effective only in ICU patients [16, 17, 22]. The American Gastroenterological Association suggests the use of goal-directed therapy for initial fluid management, which is defined as the titration of intravenous fluids to specific clinical and biochemical markers, such as the heart rate, mean arterial pressure, CVP, urine output, blood urea nitrogen, and haematocrit levels [22]. Although the use of goal-directed therapy has been shown to lower mortality in sepsis, there is some lack of evidence concerning its efficacy in reducing the rate of mortality, pancreatic necrosis, or persistent multiorgan failure (MOF) in cases of severe acute pancreatitis (SAP) [22].

The evidence regarding which type of fluid is more beneficial is weak and based more on randomized controlled trials (RCTs). Ringer's lactate solution is considered superior to normal saline, which is associated with hyperchloremic metabolic acidosis when infused in large volumes, while the use of hydroxyethyl starch fluids is no longer suggested [23, 24].

**2.2. Antibiotics.** Another commonly made mistake while managing patients with AP is abuse in the administration of antibiotics. Recent scientific data have proven that prophylactic antibiotics do not decrease mortality and morbidity rates and therefore are no longer recommended for all AP cases [16, 19, 20]. The use of antibiotics in patients with sterile necrosis as a measure to halt the development of infected necrosis is not recommended [16, 19, 20].

Antibiotics should be given for infected necrosis or extrapancreatic infection, such as bacteraemia or respiratory tract, urinary tract, abdominal, biliary tract, or wound infection [16, 19, 20, 25–28]. Because patients with AP often fulfil the criteria for systemic inflammatory response syndrome (SIRS) or the quick sequential organ failure assessment score (qSOFA) at the time of presentation, diagnosis is somewhat challenging in daily practice [25–29]. Infected necrosis

should be suspected in patients with pancreatic or extrapancreatic necrosis who show no signs of improvement after 7–10 days of hospitalization [16, 19, 20, 25–28]. In these patients, the use of either appropriate antibiotics determined based on the culture acquired from a computerized tomography- (CT-) guided fine-needle aspiration (FNA) sample or the immediate empiric use of antibiotics against both aerobic and anaerobic Gram-negative and Gram-positive microorganisms should be initiated [16, 19, 20, 25–28, 30]. The timing of infection varies from  $9.1 \pm 8.8$  days for extrapancreatic locations to  $13.9 \pm 12.3$  days for pancreatic intrusion and can reach up to  $31.6 \pm 26.4$  days in the case of a fungal contamination [25–28, 31].

The most common Gram-negative bacterial species are *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*, while the most common Gram-positive bacterial species are *Staphylococcus epidermidis*, *Enterococcus faecium*, *Staphylococcus haemolyticus*, and *Staphylococcus aureus* [32]. Antibiotics known to penetrate pancreatic necrosis should be given, such as third- or fourth-generation cephalosporins, carbapenems, quinolones, and metronidazole [16, 19, 20, 25–28]. Since the proportion of multidrug-resistant bacteria is relatively large, caution should be used in the prioritization of cultures and application of antibiotics [16, 19, 20, 25–28, 30, 31]. Even though fungal contamination with *Candida albicans* and other *Candida* spp. indicates a higher risk of mortality, the routine administration of antifungal agents concurrently with antibiotics is not recommended [16, 19, 20, 25–28, 31].

Studies have demonstrated that serum levels of procalcitonin (PCT) could be beneficial in anticipating the risk of developing infected pancreatic necrosis [33]. More precisely, C-reactive protein and PCT are markers with high sensitivity but low specificity for infected necrosis [33, 34]. As a conclusion, CT-guided FNA for strain and Gram culture remains the diagnostic tool of choice, although it has been abandoned in some centres because of the high rate of false-negative findings [16, 19, 20, 25–28, 30].

**2.3. Feeding.** Up to 2001, enteral feeding was applied in 25% of the hospitals, a status quo that changed after the

publication of an International Consensus Guideline by the American Society for Parenteral and Enteral Nutrition [35]. It is now believed that early enteral feeding lowers the rates of infective complications, MOF, SIRS, and overall mortality, as well as intra-abdominal hypertension [36–39]. Apart from the nutritional role, the anti-infectious and immunomodulatory properties of enteral feeding contribute in reducing bacterial overgrowth; strengthening intestinal barriers; preventing the adherence of pathogenic bacteria; averting the translocation of endotoxins, pancreatic enzymes, and cytotoxic mediators; maintaining the balance of intestinal flora; and regulating the proportion of natural killer cells, T-lymphocytes, and other immune cells over the intestinal mucosa [36–39]. The current guidelines support the immediate start of oral feeding with a low-fat, solid diet notwithstanding the severity of AP, unless abdominal pain, vomiting, or nausea has not resolved [16, 19, 20].

When oral feeding is not feasible, either nasogastric or nasojejunal delivery could be used with the same safety and efficacy [16, 19, 20, 40]. Routine nasogastric tube insertion is not recommended [16, 19, 20]. Total parenteral nutrition should be avoided as much as possible; thus, partial parenteral nutrition should be implemented if the enteral route is not tolerated or the patient does not meet the caloric requirements [16, 19, 20, 41].

The optimal time for the administration of enteral nutrition is still debatable. Current evidence-based data recommend initiation within the first 24 to 48 hours, while the PYTHON trial, a multicentre randomized study, pinpointed that there is no statistically significant difference in the mortality rate between early nasoenteric tube feeding within 24 hours and delayed oral feeding after 72 hours [16, 19, 20, 40].

Finally, many studies refer to the addition of probiotics in nutrition formulas [42]. While RCTs have demonstrated a beneficial role in AP, the increased mortality rate found in the symbiotic group in the PROPATRIA trial indicated the need for reassessment, as the fermentation process in the gut contributed to systematic acidosis [43]. Hence, probiotics cannot be recommended for the management of AP according to the most recent data [16, 19, 20].

**2.4. Pain Control.** Another important part of conservative treatment is pain control in patients with AP. Although there is no evidence in the available data about restrictions in pain medication, patients with AP are often undertreated, so their quality of life is compromised. This often results in delayed mobilization, respiratory distress, or avoidance of enteral feeding, which are crucial mistakes, especially for the first 24 hours. The 2019 WSES guidelines support that patient-controlled analgesia should be integrated with every possible strategy, including intravenous, epidural, and multimodal approaches [16].

Overall, the parenteral analgesics used for pain control in AP can be divided into three groups: opioid analgesics, local anaesthetics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Historically, opioids, especially morphine, have long been blamed for causing pancreatitis-associated complications because of their action in causing spasms in the

sphincter of Oddi, as well as addiction and tolerance issues [44]. However, the latest studies demonstrated that opioid analgesics could be safely administered with major benefit in AP [45]. Parenteral opioids that are frequently used include buprenorphine, pethidine, morphine, and fentanyl [45]. Several studies have been designed to compare opioid agents and their combinations in treating patients with AP. Meng et al. conducted a systematic review of the current clinical studies to assess the safety and efficacy of parenteral analgesics for pain relief in patients with AP [46]. In this study, they concluded that procaine should not routinely be used for pain relief and that morphine should be avoided in patients with AP, as it may cause spasms in the sphincter of Oddi [46]. Pethidine in combination with fentanyl was effective, but special attention must be taken to avoid adverse effects [46]. Buprenorphine, pentazocine, and NSAIDs showed better safety and efficacy [46].

The systemic administration of local anaesthetics is considered to relieve pain via anti-inflammatory, neuro-protective, and motility-modulating effects [45]. Epidural analgesia may be considered for patients who require high doses of opioids for an extended period as it was found to enhance microcirculatory perfusion and end-organ perfusion and improve survival rates [47].

**2.5. Imaging.** Additionally, the proper management of AP includes the proper use of cross-sectional imaging as a diagnostic tool. The diagnosis of AP can be determined on admission using ultrasound (U/S) to identify the aetiology of AP [16–20]. These imaging data, in combination with the consistent clinical presentation and an elevated serum amylase and/or lipase level greater than three times the upper limit of normal, establish a definite diagnosis [16–20]. For this reason, CT scans are not required in the majority of patients.

The current guidelines recommend ideally performing a CT scan 72–96 h after the onset of symptoms [16–20]. First and foremost, an early CT scan will most likely not reveal any necrotic or ischemic areas in the pancreas, which may not be visible for several days, and subsequently will not change the clinical management, length of hospitalization, or therapeutic scheme [48–51]. Second, even though CT scans are very useful in the identification of pancreatic complications, the quantification of pancreatic necrosis and peripancreatic fluid collections, and the stratification of disease severity, the repeated applications increase the total radiation dose [48–51]. It is suggested that additional CT scans should be performed upon deterioration of the clinical status [16–20, 48–51]. Third, caution should be applied in patients with SAP as contrast-enhanced imaging could contribute to the development of acute kidney injury [52]. Last but not least, the overuse of diagnostic CT scans escalates healthcare expenditures and excessively depletes healthcare resources [48–51]. However, CT should be performed as a means to exclude from differential diagnosis perforating peritonitis, mesenteric ischaemia, active haemorrhage, and thrombosis, as well as in cases of diagnostic dilemma [16–20, 48–51].

In the event of allergies to contrast or renal impairment or in young or pregnant patients, a T2-weighted magnetic

resonance imaging scan or a CT scan without contrast is indicated [53]. Magnetic resonance cholangiopancreatography (MRCP) or endoscopic U/S (EUS) should be considered, provided that transabdominal U/S is not indicative of gallstones or biliary obstruction in the absence of cholangitis or abnormal liver function tests [16, 19, 20, 53].

### 3. Endoscopic and Surgical Approaches without Pancreatic Necrosis

**3.1. ERCP.** The timing and indications for endoscopic retrograde cholangiopancreatography (ERCP) in cases of AP are crucial. ERCP is not recommended in patients with acute gallstone pancreatitis (AGP) without cholangitis [16–20]. Compared to conservative treatment, ERCP has no impact on critical outcomes, such as mortality, single-organ failure, or necrosis [54]. When cholangitis is present, early routine ERCP (within 24 hours of admission) significantly reduces mortality as well as local and systemic complications [16–20]. Patients with biliary obstruction benefit from early ERCP, with a significant reduction in mortality [16–20]. In those cases, the differential diagnosis between acute cholangitis and pancreatitis with SIRS may be difficult, and as a result, every effort should be made to identify biliary obstruction, including MRCP or EUS, before performing ERCP [54]. Guidewire cannulation of the common bile duct compared with conventional contrast cannulation, the placement of a 3 Fr pancreatic duct stent in high-risk patients, and the post-ERCP placement of rectal NSAIDs appear to prevent post-ERCP worsening of pancreatic inflammation [55, 56].

The role of early ERCP and sphincterotomy in preventing major systematic complications in cases of severe AGP without cholangitis was controversial for a long time. Data from RCTs have failed to answer whether such an approach was superior to conservative treatment. The APEC trial, which was a multicentre randomized trial, was designed for this purpose [57]. The results depicted that in patients with predicted severe gallstone pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment [58].

**3.2. Cholecystectomy.** Another common question among surgeons is the timing of cholecystectomy in patients with biliary pancreatitis. Current guidelines recommend laparoscopic cholecystectomy in patients with mild gallstone pancreatitis within the same index admission [16, 20]. Laparoscopic cholecystectomy is considered safe for these patients and should be performed early during the hospital stay, as long as the patient is clinically improving, to decrease the length of stay and the overall costs [16, 59, 60]. In addition, there is no difference in the need for conversion to open surgery, duration of surgery, or complication rate between performing cholecystectomy during the hospital stay for mild pancreatitis and performing cholecystectomy some weeks after the discharge of the patient [59, 60]. Furthermore, intraoperative cholangiography can be performed and any remaining bile duct stones can be treated with postoperative or intraoperative ERCP [16, 20].

In patients with mild pancreatitis due to gallstones who cannot undergo surgery, such as elderly patients and patients with severe concomitant comorbidities, biliary sphincterotomy alone may be an effective way to reduce further episodes of AP, although cholecystitis may still occur [61]. When ERCP and sphincterotomy have been performed previously for AGP combined with acute cholangitis, cholecystectomy during the same admission in the hospital is still advised, as the risks of recurrent biliary events become diminished [16, 20].

In patients with moderate to severe AGP, cholecystectomy should be delayed for some weeks after the discharge of the patient from the hospital [16, 20]. The reason for that is the existence of peripancreatic fluid collections and potentially pseudocysts. The cholecystectomy should be postponed until the fluid collections and pseudocysts resolve or have been determined to be persistent and walled off [16, 20]. Nealon et al., in a retrospective study, evaluated the safety of delayed versus early cholecystectomy in this group of patients [62]. They reported that cholecystectomy during the admission of the patient for AP may be followed by a second surgery in case pancreatic collections do not resolve and surgical pseudocyst drainage is required [62]. Furthermore, infectious complications are common when cholecystectomy is performed sooner than 3 weeks after SAP and a 6-week interval after identifying a pseudocyst is a reasonable time period to await possible spontaneous resolution or adequate organizing of the cyst wall [62]. No patient participating in this study had recurrent episodes of AP in this 6-week period, so the authors proposed cholecystectomy 6 weeks after the onset of SAP [62].

### 4. Endoscopic and Surgical Approaches with Pancreatic Necrosis

In case of pancreatic necrosis, any surgical or endoscopic intervention should be avoided and conservative management should be followed until necrotic collections become organized, usually four weeks after the onset of pancreatitis [16–20]. The mortality rate after intervention before four weeks can reach up to 78% versus 28% in patients treated conservatively [63]. It is widely accepted that late intervention results in a significant survival benefit, causing fewer injuries to vital tissues and less bleeding [16–20, 63]. If urgent surgery is needed earlier than four weeks for other indications, such as abdominal compartment syndrome (ACS) or bowel necrosis, necrosectomy is not recommended [16–20, 63].

The majority of patients with sterile necrosis can be managed without intervention [16–20, 63, 64]. Ongoing organ failure without signs of infected necrosis, ongoing gastric outlet, biliary or intestinal obstruction from a large, walled-off necrotic collection, disconnected duct syndrome, and symptomatic or growing pseudocysts are indications for drainage four weeks after the onset of AP, while ongoing pain or discomfort after eight weeks is also another criterion. [16–20, 63–65]. Furthermore, strong suspicion of infected necrotizing pancreatitis with clinical deterioration is a sign for intervention after four weeks [16–20, 63–65].

TABLE 4: Advantages and disadvantages of each minimally invasive technique.

Percutaneous approach	Endoscopic approach	VARD	Laparoscopic approach
Multiple attempts	Multiple attempts	One attempt	One attempt
Complication rate: 20% and mortality rate: 28%	Complication rate: 28% and mortality rate: 5.6%	Complication rate: 17.5% and mortality rate: 2.5%	Conversion to open surgery < 20% and mortality rate: 10%
Complications: intra-abdominal haemorrhage, colonic perforation, intestinal fistula, and pancreatic fistula	Complications: bleeding, perforation of abdominal cavity, and peritonitis	Complications: colonic fistula, gastric and duodenal perforation, enteric fistula, pancreatic fistula, and retroperitoneal haemorrhage	Complications: pancreatic fistula, recollection, and bleeding
Anesthesia: general or sedation	Anesthesia: general or sedation	Anesthesia: general	Anesthesia: general
Suitable for collections in the left pancreas	Suitable for collections in the retrogastric space in contact with the posterior wall of the stomach	Suitable for collections in the body and tail of the pancreas	Suitable for all collections
Suitable for solid collections	Suitable for predominant fluid collections	Suitable for solid collections	Suitable for predominant fluid collections
Possible in unstable patients	The patient's condition must be stable	Possible in unstable patients	The patient's condition must be stable
Single used method: 44% and need for surgical treatment: 56%	Single used method: 60% and need for surgical treatment: 20%–28%	Single used method: 81% and need for surgical treatment: 19%	Single used method: 80% and need for surgical treatment: 20%
References: [66–72].			

**4.1. Minimally Invasive Techniques.** In case of intervention, the current guidelines recommend that a step-up approach with minimally invasive techniques must be adopted firstly and before any surgical procedure [16, 19, 20]. The preferred strategy includes four main minimally invasive procedures: minimally invasive percutaneous necrosectomy (MIPN), endoscopic transmural necrosectomy (ETN), laparoscopic necrosectomy (LN), and video-assisted retroperitoneal debridement (VARD) [66, 67]. All methods share a common concept of achieving minimally invasive sepsis control while maintaining adequate nutritional competence [66, 67]. The choice of one approach over another depends on the anatomical position and the relation of necrotic debris with adjacent organs, the maturation of the surrounding wall, the composition of necrotic collections, the clinical condition of the patient, and the expertise of the surgeon, the endoscopist, or the radiologist participating in the procedure [66, 67] (Table 4).

Based on a recent systematic review and meta-analysis of the literature, these minimally invasive approaches were shown to be relatively safe, as complications occurred in 21.3% of the pooled population [68]. The most common complications related to these techniques are haemorrhage, hollow viscus perforation, solid organ injury, and enterocutaneous fistula formation, while new-onset MOF, pulmonary, cardiac or renal failure, disseminated intravascular coagulopathy, and new-onset diabetes may also occur [68, 69].

When MIPN is performed, drainage occurs under CT guidance and a percutaneous catheter (usually 10–12 F) is inserted into the necrotic collection using the standard Sel-

dinger technique [66, 67]. Once access to the collection is established, a balloon dilator is inserted, a nephroscope (flexible endoscope or laparoscope) is positioned via the Amplatz sheath, and necrosectomy is performed using a combination of lavage and debridement under direct vision [66, 67]. The nephroscope has an operating channel that permits standard (5 mm) laparoscopic graspers as well as an irrigation/suction channel [66, 67]. At the end of the procedure, an 8 F catheter sutured to a 24 F drain is passed into the cavity to allow continuous postoperative lavage [66, 67]. A number of approaches may be employed, depending on the size and position of the necrotic collection, including the transhepatic, posterolateral (between the left kidney and colon), and right-sided routes [66, 67].

VARD is performed with the patient placed in a supine position with the left side elevated by 30–40° [66, 67, 70]. A subcostal incision of 5 cm is placed in the left flank at the midaxillary line, close to the exit point of the percutaneous drain [66, 67, 70]. Using the in situ percutaneous drain as a guide, the retroperitoneal collection is entered [66, 67, 70]. The cavity is cleared of purulent material using a standard suction device [66, 67, 70]. Visible necrosis is carefully removed with the use of long grasping forceps [66, 67, 70]. Deeper access may be facilitated using a 0° laparoscope, and further debridement may be performed with laparoscopic forceps under videoscopic assistance [66, 67, 70]. Drains are positioned in the cavity, providing a continuous postoperative lavage system, and the fascia is closed [66, 67, 70]. With this method, an extensive removal of infected necrotic tissue is achieved [66, 67, 70].

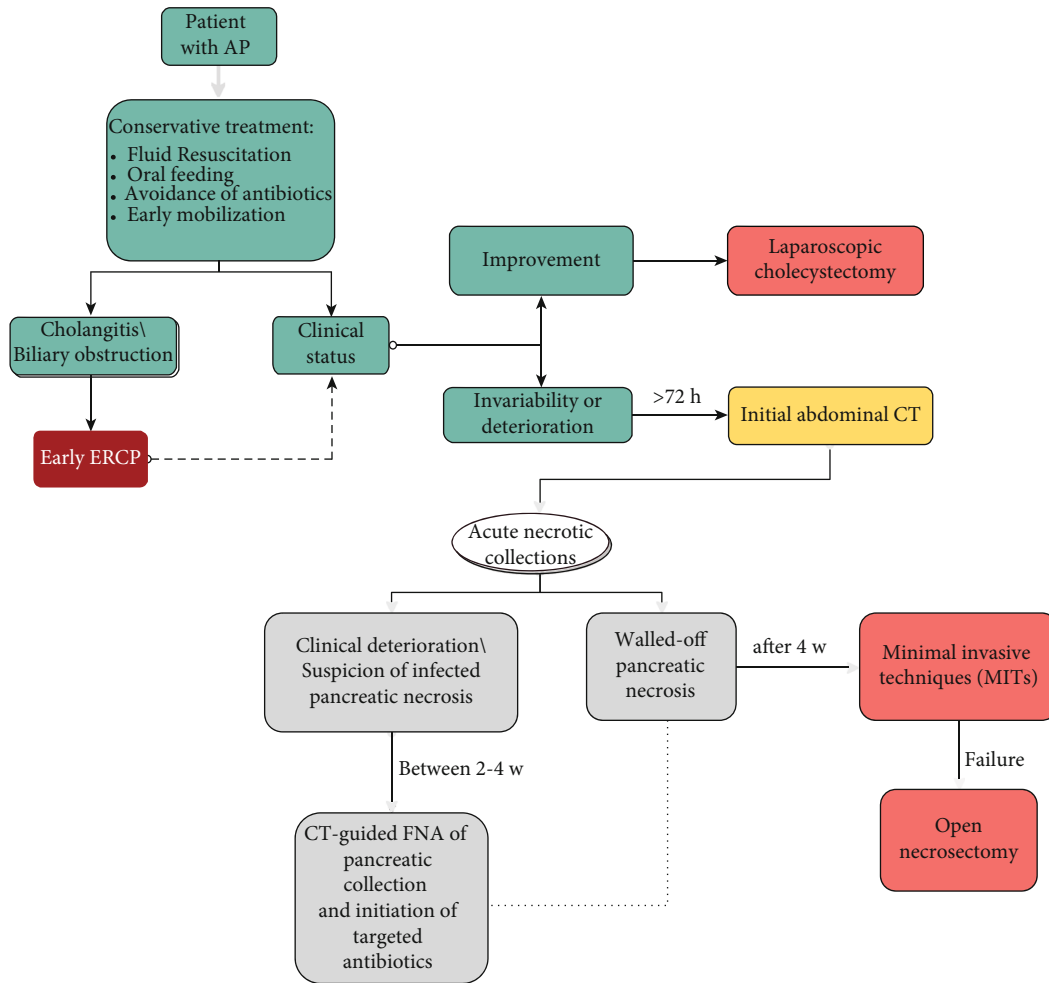


FIGURE 1: Algorithm for the treatment of acute biliary pancreatitis.

There is considerable variation in laparoscopic techniques, although the two main methods involve either a full laparoscopic procedure undertaken under CO<sub>2</sub> pneumoperitoneum or a modified laparoscopic procedure aided by the placement of a hand port [67, 71]. In a clinically well patient with established walled-off necrosis, LN may offer the potential for a single intervention with the possibility of simultaneous definitive management of cholelithiasis, as cholecystectomy can be performed with safety [67, 71]. This method is not possible when severe abdominal hypertension exists, and for that reason, it constitutes the least of minimally invasive techniques in use [67, 71]. On the contrary, LN is adequate for the drainage of multiple infected areas in a single procedure [67, 71].

ETN is a novel approach that is aimed at further minimizing damage to the surrounding tissues [67, 68]. In endoscopic necrosectomy, EUS is used to localize the collection and at excluding the major vessels [67, 68]. Typically, a transgastric puncture is made to enter the cavity [67, 68]. The track is dilated, and the scope is used to achieve irrigation and drainage of debris [67, 68]. A pigtail stent may be laced endoscopically and left in the cavity [67, 68].

Compared with other minimally invasive procedures, ETN has fewer complications related to the abdominal wall.

More precisely, the incidence of external pancreatic fistula, incisional hernia, and wound infection is significantly lower [72]. This method is performed only in a few centres due to complexity and the lack of experience [72].

**4.2. Open Necrosectomy.** Open surgery should be considered when endoscopic or percutaneous methods are not effective or when complications occur while performing minimally invasive techniques [16, 19, 20, 63, 64]. Other indications for open surgery are severe complications of the disease, including ACS, bowel ischaemia, or perforation due to necrosis, acute necrotizing cholecystitis, and bowel fistula formation extending into the pancreatic collection [16, 19, 20, 63, 64]. Finally, a lack of sufficient experience for minimally invasive techniques is another criterion for open surgery [16, 19, 20, 63, 64].

When open necrosectomy is performed, an upper transverse subcostal laparotomy is implemented because it provides better exposure of affected necrotic areas, unless the patient has already undergone surgery for the treatment of ACS or bowel resection and a middle laparotomy has already been used [63, 64]. Pancreatic and peripancreatic necrosis are approached through the gastrocolic ligament, and necrosectomy is performed using blunt trauma dissection assisted with

careful suction to avoid trauma to vital tissues [63, 64]. In the presence of retrocolic or retromesenteric necrosis, these areas can be approached lateral to the ascending or descending colon with or without mobilization of the hepatic or splenic flexure [63, 64]. However, mobilization of the colon should not be performed if not necessary because of the risk of iatrogenic injury [63, 64]. Microbiological samples from necrotic tissue are routinely taken during surgery [63, 64]. After debridement of all necrotic tissues, lavage with normal saline is completed and drains are placed into the cavity [63, 64]. In addition to necrosectomy, cholecystectomy may be performed in patients with biliary pancreatitis [16, 63, 64].

The risk of mortality in open necrosectomy depends on patients' preoperative risk factors such as age over 60 years, pre-existing comorbidities, MOF, white blood cell count over  $23 \times 10^9$ , and the interval from symptom onset [63, 64]. The most important agent is the time period between the beginning of disease and surgery. The mortality rate becomes diminished, from 23% to 11%, if necrosectomy is delayed until 4 weeks and the necrosis has become walled off on preoperative imaging. In patients with organized necrosis and without risk factors, open necrosectomy may be performed with a minimal mortality rate [63, 64].

Another technique for debridement, which mainly addresses to disconnected left pancreatic remnants, is transgastric necrosectomy. The main steps of this single-stage surgical procedure, which can be performed either laparoscopically or openly, is the exposure of the gastric cavity through an anterior gastrotomy and the junction of the posterior gastric wall with the adherent anterior fibrous wall of necrotic collection. In this way, a common channel is created through the stomach and the cavity of pancreatic debris. Driedger et al., in 178 cases of walled-off necrosis, reported a postoperative mortality rate of 2% in patients treated with this approach [73]. Although transgastric necrosectomy was associated with excellent outcomes, including symptom resolution in a percentage ratio of 91%, a short postoperative length of hospital stay, and a high discharge rate, these patients exhibited significant rates of postoperative morbidity and recurrence, 38% and 20%, respectively [73].

## 5. Conclusions

The burden of AP is a plague of the 21<sup>st</sup> century, requiring much attention in its management [1, 16–20]. The mortality rate of AP in its severe form can reach up to 20%, which constitutes the extremely important appropriate treatment of the disease in its early phase [1, 2, 74]. The first 24–72 hours from the onset of the disease are crucial, and the initial conservative treatment should be swift, accurate, and in accordance with recent scientific data so as to avoid pancreatic necrosis.

In case of pancreatic necrosis, any intervention should be postponed until necrotic collections become organized, usually four weeks after the onset of pancreatitis [16–20]. In case of intervention, the current guidelines recommend that a step-up approach with minimally invasive techniques must be adopted firstly and before any surgical procedure [16, 19, 20]. Several studies have attempted to compare the two methods. Minimally invasive approaches appear to have, in

comparison with open necrosectomy, lower rates of pancreatic fistula formation, early postprocedural organ dysfunction, mortality, and long-term complications, such as hernias, exocrine pancreatic insufficiency, and use of antidiabetic medication [69, 75, 76]. On the other hand, minimally invasive procedures have been criticized, as they often require repeated debridement attempts prior to resolution, prolonging the inpatient stay [63, 64, 69, 75, 76].

There is no panacea for treating AP. New experimental models and the use of genetically engineered animals have produced data that contribute to the state-of-the-art knowledge about the pathophysiology and possible prevention and treatment options of the disease [77, 78]. Potential therapeutic agents are currently undergoing investigation in preclinical and early clinical trials [1, 2, 77]. There is a crucial necessity to exploit the advances in genome-wide association studies and design better genetically engineered animal models to unravel new, unidentified susceptibility and pathogenicity loci for pancreatitis to achieve a better understanding of the genetic and epigenetic basis of the disease [1, 2, 77, 78]. Ultimately, there is a need to build collaborative, multi-centre networks, conduct large-scale clinical trials, and constantly reassess guidelines with the aim of improving the management and prognosis of patients with AP [1, 2, 77, 78]. Prior to reaching a final cure, we should ensure that precise management strategies for AP are being followed and frequent errors are being avoided (Figure 1).

## Abbreviations

AP:	Acute pancreatitis
ICU:	Intensive care unit
WSES:	World Society of Emergency Surgery
CVP:	Central venous pressure
MOF:	Multiorgan failure
SAP:	Severe acute pancreatitis
RCTs:	Randomized controlled trials
SIRS:	Systemic inflammatory response syndrome
qSOFA:	Quick sequential organ failure assessment
CT:	Computerized tomography
FNA:	Fine-needle aspiration
PCT:	Procalcitonin
NSAIDs:	Nonsteroidal anti-inflammatory drugs
U/S:	Ultrasound
MRCP:	Magnetic resonance cholangiopancreatography
EUS:	Endoscopic ultrasound
ERCP:	Endoscopic retrograde cholangiopancreatography
AGP:	Acute gallstone pancreatitis
ACS:	Abdominal compartment syndrome
MIPN:	Minimally invasive percutaneous necrosectomy
ETN:	Endoscopic transmural necrosectomy
LN:	Laparoscopic necrosectomy
VARD:	Video-assisted retroperitoneal debridement.

## Data Availability

Previously reported data were used to support this study. These prior studies are cited at relevant places within the text as references.



## Conflicts of Interest

The authors declare no conflicts of interest.

## Authors' Contributions

All authors contributed to the study conception and design. The research in the PubMed database was performed by MG, IG, AM, ET, EK, AS, and EM. The analysis of the articles found in the PubMed database was performed by MG, IG, AM, ET, EK, AS, and EM. MC supervised the project. The first draft of the manuscript was written by MG, IG, and AM in consultation with MF and KS. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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