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REVIEW

Treatment of acute pancreatitis

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ABSTRACT

Acute pancreatitis (AP) is a potentially life-threatening inflammatory condition characterized by localized pancreatic damage and the activation of the inflammatory cascade, leading to systemic inflammatory response syndrome (SIRS). This complex disease often presents with a variable and unpredictable course. The primary causes of AP include the migration of gallstones and alcohol consumption. The Revised Atlanta Classification 2012 (RAC) is the most widely utilized classification system for AP, distinguishing between interstitial edematous pancreatitis and necrotizing pancreatitis, three severity levels and an early and a late phase. Severe AP carries a high risk of mortality. Currently, there is no definitive prognostic score for accurately predicting severe cases of AP. Initial management focuses on supportive care, applicable to both mild and severe forms of the disease, while later management addresses complications associated with severe AP. Although there is no consensus on the optimal type or regimen of fluids for resuscitation, goal-directed fluid therapy, particularly with Ringer's lactate, has been linked to improved outcomes. Prophylactic antibiotics have not proven effective in preventing infectious complications associated with AP. Patients experiencing mild acute gallstone pancreatitis should be advised to undergo laparoscopic cholecystectomy during their initial admission, whereas those with severe gallstone pancreatitis and signs of cholangitis or choledocholithiasis may benefit from early endoscopic retrograde cholangiopancreatography (ERCP). The management of severe AP complications has evolved from an early surgical approach to a minimally invasive step-up strategy, which is now considered the standard intervention.

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KEY WORDS: Pancreatitis; Etiology; Complications; Drainage; Minimally invasive surgical procedures; Open abdomen techniques.

Acute pancreatitis (AP) is a frequent inflammatory condition affecting the exocrine pancreas, marked by the premature activation and leakage of digestive enzymes. This leads to local pancreatic damage and triggers an inflammatory response, which can result in systemic inflammatory response syndrome (SIRS). AP is characterized by a rapid onset of symptoms and a variable clinical trajectory that can be challenging to predict in its early stages, with an overall mortality rate ranging from 1% to 5%.[1, 2] There are two main classification systems for AP: the Determinant-Based Classification of Acute Pancreatitis Severity (DBC) and the Revised Atlanta Classification (RAC) from 2012, with the RAC being the more widely utilized. The RAC catego-

rizes AP into two forms (interstitial edematous pancreatitis and necrotizing pancreatitis) and further classifies the disease by severity into mild, moderately severe, and severe categories, as well as phases, distinguishing between early (<1 week) and late (>1 week) stages.[3] The severity of AP is associated with the presence or absence of local complications and organ failure, with mild cases showing no complications, moderately severe cases exhibiting transient organ failure, and severe cases featuring persistent organ failure. Histologically, AP is classified into three types: type 1 necrosis, which primarily affects the surrounding fatty tissues; type 2 necrosis, characterized by necrosis predominantly involving ductal structures; and type 3 necrosis, which targets acinar cells.[4, 5] In cases of AP without post-necrotic gland damage, patients may experience a full recovery of histological and physiological functions, provided the underlying cause is addressed. The primary causes of AP include gallstones (40-65%), alcohol consumption (25-40%), and a variety of other factors (10-30%) such as hypertriglyceridemia, smoking, medications, autoimmune conditions, and genetic predispositions.[6-8] However, the exact pathogenic mechanisms of AP are not yet fully understood and require further investigation to enhance treatment options. Diagnosis and assessment of AP severity and prognosis rely on clinical presentation, laboratory results (such as serum amylase and lipase levels), various scoring systems, and imaging techniques like contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and ultrasound (US). Approximately 80% of patients experience mild to moderately severe forms of the disease, while about 20% develop severe AP, which can lead to necrosis of pancreatic or peripancreatic tissue and potential organ failure.[9-11] Despite a generally low mortality rate, severe AP cases can result in significant morbidity, with mortality rates estimated at 4-5% for mild cases and 30-50% for severe cases,[12-14] leading to an overall mortality of up to 6%.[12] Recent treatment guidelines for AP have evolved significantly, emphasizing minimally invasive therapies and a multidisciplinary approach, alongside a step-up strategy for management.

Literature search strategy

To retrieve the articles, an extensive literature search was performed using the databases of Medline through PubMed, Scopus, and Google Scholar from January 2000 to September 2024. The search terms were "acute pancreatitis," "pancreatitis," "management of pancreatitis," "severe acute pancreatitis." Particular emphasis was given to guidelines of medical and surgical societies, systematic reviews and meta-analysis. Manual search was also performed on numerous textbooks of medicine, surgery, gastroenterology, and critical care. Limitations of this review included the only inclusion of published studies, articles published in English and the lack of systematic comparison between studies. Nonetheless, we aimed at helping to identify gaps in the existing knowledge and providing a context for future research in the management of AP.

Epidemiology

The incidence of AP has been rising at a rate of 2% to 5% annually, with global rates ranging from 3.4 to 110 cases per 100,000 individuals.[15, 16] This incidence varies by geography and age. In the USA, the estimated annual incidence of adult AP is about 40 cases per 100,000 people.[17] In Europe, figures for adult AP range from 4.6 to 100 per 100,000 individuals.[18] Longitudinal studies from Japan reveal a threefold increase in incidence from 1998 to 2011, with a prevalence of 49.4 cases per 100,000 adults.[19] Additionally, the likelihood of developing AP increases with age, particularly during the fifth and sixth decades of life, and it is observed to be 10% to 30% more common in men than in women.[20] Currently, AP stands as one of the leading causes of hospitalization for gastrointestinal disorders. In the Unites States, nearly 300,000 hospital admissions occur annually due to AP, resulting in over 1 million patient days in hospitals and exceeding a cost of 2.5 billion dollars.[7, 8]

Etiology

There are multiple causes and pathological conditions potentially associated with AP, but in some cases the cause of AP cannot be detected

TABLE I.—*Etiology of acute pancreatitis.*

Category	Causes of acute pancreatitis
Metabolic factors	Alcoholism Hyperlipidemia Hypertriglyceridemia Hypercalcemia Drugs (medicaments)
Mechanical factors	Gallstones, biliary sludge Tumors (pancreatic tumor, villous tumors of the ampulla) Pancreatic trauma Adhesions due to previous surgical procedures Injuries during endoscopic procedures (ERCP, biopsy) Pancreas divisum
Vascular causal factors	Thrombosis Embolism Systemic vasculitis
Infectious agents	Viruses: SARS-CoV-2, hepatitis viruses, EBV, CMV, HSV, VZV, coxsackie virus, mumps, HIV Bacterial agents: *Escherichia coli*, yersinia, legionella, mycoplasma, salmonella Fungi: aspergillus
Infectious pathogens	Parasites: ascaris lumbricoides, cryptosporidium, toxoplasma, clonorchiasis
Other factors	Immune-mediated Genetic (trypsinogen mutations) Idiopathic pancreatitis

despite all diagnostic modalities, and such AP is labelled as idiopathic. Known causes of AP are grouped into four main groups: metabolic, mechanical, vascular and infectious (Table I).

Metabolic factors

Metabolic factors include alcoholism, hyperlipidemia, hypertriglyceridemia, hypercalcemia (hyperparathyroidism represents one of the main causes of recurrent AP) and numerous drugs such as furosemide, azathioprine, tetracyclines.

Mechanical factors

Mechanical factors contributing to acute pancreatitis include trauma to the pancreas (which accounts for less than 1% of cases), obstruction from biliary calculi, microliths, and tumors (such as pancreatic tumors or villous tumors of the ampulla). Other factors include pancreas divisum, adhesions from previous surgeries, and injuries resulting from endoscopic procedures like endoscopic retrograde ERCP-and biopsies. These obstructions in the pancreatic ducts can lead to ductal hypertension, potentially causing the rupture of smaller ducts and resulting in the leakage of pancreatic juice into the pancreatic tissue itself.

Vascular causal factors

Vascular causal factors are primarily thrombosis, embolism and systemic vasculitis, which can lead to pancreatic ischemia.

Infectious agents

Among the infectious agents (<1%), viral hepatitis A, hepatitis B, hepatitis C, Coxsackie, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and mumps virus stand out. From bacterial agents Escherichia coli, Yersinia and Legionella. One of the infectious pathogens to think about is Ascaris lumbricoides, which is especially important for the climates in which it resides.

Other causes

In addition to the causes reported above, the etiology of AP can be immune-mediated, or related to genetic abnormalities regarding trypsinogen mutations or anatomical structures (the most significant of which is the pancreas divisum where the junction of the ventral and dorsal canals is absent).[21]

Diagnosis

According to the RAC 2012, diagnosing AP necessitates the presence of at least two of the following three criteria: 1) abdominal pain consistent with AP, typically characterized by a sudden onset of severe, persistent epigastric pain that may radiate to the back; 2) serum lipase (or amylase) levels that are at least three times above the upper limit of normal; and 3) characteristic findings on CECT, MRI, or transabdominal US.[3] It is noteworthy that relying solely on two of these criteria can miss about 25% of AP cases and could result in misdiagnosis in about 10% of patients.[1] Clinicians must maintain a high index of suspicion when diagnosing AP, taking into account the patient's medical history, symptoms,

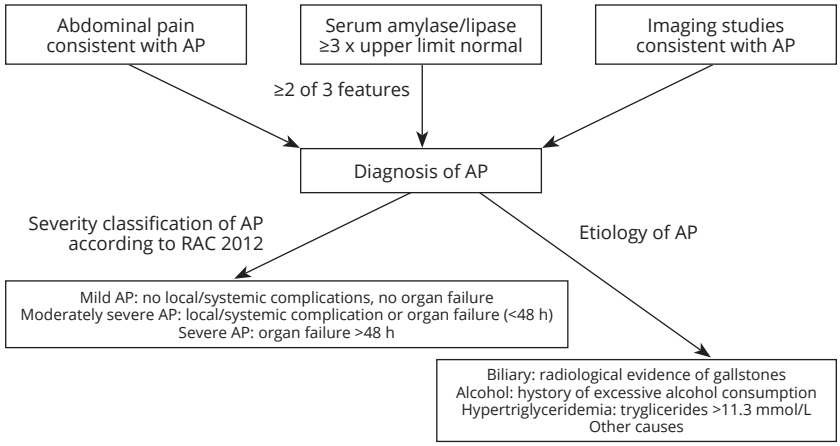

Figure 1.—Initial diagnosis and severity classification of AP.

physical examination, laboratory tests, and imaging studies. Initial evaluations should prioritize identifying past episodes of AP and associated risk factors, such as gallstone disease, alcohol consumption, family history of pancreatitis, recent infections, trauma, insect bites, and new medications (Figure 1).

Clinical aspects

Abdominal pain is the predominant symptom, experienced by 80-95% of patients, and can be localized to the mid-epigastrium or spread throughout the abdomen. This pain is typically described as constant, often worsening with eating, drinking, or lying flat, and may radiate to the back, with relief sometimes found by sitting or leaning forward. Additional symptoms may include nausea, vomiting, tachycardia, and low to moderate fever. Jaundice can occur if the common bile duct is obstructed due to gallstones or pancreatic edema. In severe cases, shock may develop. Physical exams often show abdominal distension and decreased bowel sounds, while rebound tenderness is rare due to the pancreas retroperitoneal location.

Biochemical markers

Common laboratory markers for diagnosing AP include serum amylase and lipase, triglycerides, a lipid panel, complete blood count, renal and liver function tests, glucose, HbA1c, and calcium. While amylase has traditionally been used, lipase is more sensitive and specific for confirming AP. Amylase typically normalizes within 3-5 days, whereas lipase may take 8-14 days. Elevated serum levels of amylase and lipase support a clinical suspicion of AP, although amylase also derives from the salivary glands, with only about 40% coming from the pancreas.[22] Studies show that serum amylase has a sensitivity of 72% and specificity of 99% at a cutoff of three times the upper limit of normal,[23] while serum lipase ranges from 64% to 100% for sensitivity and 99% to 100% for specificity.[24] Other conditions, such as bowel obstruction, infarction, cholecystitis, or perforated ulcers, can also cause elevated amylase and lipase levels. The lipase/amylase ratio may help determine whether alcohol is the cause of AP.[25] Transaminases are primarily used to differentiate between biliary causes and other factors. An alanine aminotransferase level above 150 IU/L during an AP episode may indicate a biliary origin.[26] Elevated direct bilirubin or alkaline phosphatase can suggest choledocholithiasis. Urinary amylase is less sensitive (83%) and specific (88%) than serum amylase, but urinary trypsinogen-2 has a negative predictive value of 99%, making it a reliable marker for diagnosing AP and indicating extra-pancreatic inflammation.

Differential diagnosis

The differential diagnosis for these symptoms is extensive, including conditions such as biliary colic, perforated gastric or duodenal ulcers, bowel obstruction, mesenteric ischemia, aortic aneurysm or dissection, and inferior wall myocardial infarction.

Imaging and radiological classifications

Imaging plays a crucial role in confirming the clinical diagnosis, determining the cause, excluding alternative pain sources, and assessing the severity of AP. US is recommended as the initial imaging modality for suspected AP, helping to confirm or rule out the diagnosis and identify possible underlying causes. CECT and MRI are beneficial for detecting local complications and evaluating pancreatic necrosis or severity. While US effectively identifies gallstones (over 95% sensitivity), it is less sensitive for detecting choledocholithiasis (50-80%).[26] The pancreas, situated retroperitoneally, can be challenging to visualize via ultrasound in AP. This difficulty is often exacerbated by factors such as bowel gas, the patient's body habitus, and the acute nature of abdominal pain. In mild cases of AP, US may even appear normal, and it cannot reliably differentiate between interstitial and necrotizing pancreatitis due to its inability to assess parenchymal perfusion. For gallstone assessment, it is recommended to conduct at least two high-quality ultrasound examinations. If the first examination is negative for gallstones, a subsequent ultrasound is the most sensitive method for detecting any that may have been missed. Various modified ultrasound techniques, including color Doppler US, contrast-enhanced US (CEUS), and endoscopic ultrasound (EUS), can provide additional diagnostic insights. Color Doppler US is useful for evaluating vascular complications like false aneurysms or portal vein thrombosis, while CEUS improves specificity in visualizing pancreatic edema, necrosis, and fluid collections due to its ability to highlight vessels after contrast injection. CEUS is a reliable method for diagnosing and monitoring AP, although it may not be available in emergency settings. EUS offers a minimally invasive approach and has a higher sensitivity (100%) for detecting gallstones compared to standard US (50-80%).[27] It is particularly effective for investigating microlithiasis, a known cause of recurrent AP, when other imaging fails to identify choledocholithiasis. EUS can also assess ductal abnormalities. For severity assessment and complication identification, computed tomography (CT) is the preferred imaging modality. It provides high spatial resolution and rapid acquisition, offering superior detail of pancreatic pathology compared to US. Typical CT findings in AP include pancreatic enlargement, edema, uneven density, peripancreatic fat stranding, and fluid collections. In the early phase (within the first week), CT can clarify the diagnosis and elucidate AP etiology, particularly in cases with clinical deterioration or lack of improvement. However, during the first 24-48 hours, CT may show equivocal findings for necrosis, as only 25% of patients develop it within this timeframe. The full development of pancreatic necrosis usually takes several days, and accurate assessment requires imaging at least 7 days post-onset. CT is considered the gold standard for imaging in AP due to its effectiveness and availability, especially if clinical symptoms do not improve within 48-72 hours.[28, 29] In the late phase of AP, CT is useful for monitoring established pancreatic collections and identifying complications. However, limitations include challenges in distinguishing small amounts of necrotic tissue or fat debris and potential radiation risks from multiple follow-up scans.[27] Additionally, CT may struggle to differentiate between acute peripancreatic fluid collections and necrosis, potentially leading to underestimations of complications.[22] Radiological imaging plays a crucial role in assessing the severity of acute pancreatitis (AP) through the Computed Tomography Severity Index (CTSI), which helps predict patient outcomes in terms of morbidity and mortality. The CTSI works by combining the Balthazar score, which evaluates the extent of pancreatic inflammation and fluid collections, with the CT scan assessment of pancreatic necrosis, providing a numerical score. The CTSI is highly sensitive (92%) and has perfect specificity (100%).[30] The Balthazar score consists of six categories for grading AP: A) normal pancreas (0 points), B) pancreas enlargement (1 point), C) inflammation in the pancreas and surrounding fat (2 points), D) a single ill-defined peripancreatic fluid collection (3 points), and E) two or more ill-defined peripancreatic fluid collections (4 points). Pancreatic necrosis is categorized into four levels: a) none (0 points), b) ≤30% (2 points), c) >30-50% (4 points), and d) >50% (6 points). The CTSI can yield a maximum score of

10 points: scores from 0-3 suggest mild AP, 4-6 indicate moderate AP, and 7-10 represent severe AP. Despite its usefulness, the CTSI has limitations, such as not accounting for extrapancreatic or vascular complications, and it is subject to interobserver variability, partly due to challenges in evaluating the degree of necrosis and inflammation in the pancreas.[30]

MRI serves as a valuable alternative to CT, offering superior soft-tissue contrast and enhanced evaluation of the biliary tree and pancreatic duct. MRI can help diagnose complications and determine the severity of AP, especially when CT results are negative but clinical suspicion remains high. Fat-saturated turbo spin echo T2-weighted or diffusion-weighted imaging sequences can reveal subtle inflammatory changes. MRI is particularly advantageous for patients who cannot receive iodinated contrast due to renal failure or allergies, and it is safer for pregnant patients. However, MRI is less sensitive than CT for detecting gas in fluid collections.[24, 31, 32] Magnetic resonance cholangiopancreatography (MRCP) has emerged as a reliable method for evaluating the biliary and pancreatic ducts, being particularly effective for diagnosing choledocholithiasis, though it is slightly less sensitive than EUS. Limitations of MRCP include contraindications in patients with metal implants, longer acquisition times, and challenges with scanning critically ill patients. Current guidelines from the World Society of Emergency Surgery (WSES)[29] and the American Gastroenterological Association (AGA)[33] advocate for early US in suspected AP cases to determine biliary etiology, with further imaging (repeat US, MRI, or EUS) recommended if AP is deemed idiopathic.[32, 34] In patients who do not improve after 48-72 hours, CT or MRI should be employed to assess for local complications such as pancreatic necrosis.[34] The WSES guidelines recommend that all patients with severe AP undergo CECT or MRI, ideally 72-96 hours after symptom onset, and suggest MRCP or EUS for occult common bile duct stones in unexplained cases.[29, 35]

Prediction of severity and outcomes

AP can range from mild to fulminant forms and has been noted as a cause of sudden death. The outcome of an acute episode is influenced both by the underlying cause and the severity of the attack. It is widely recognized that mortality from AP exhibits a bimodal pattern: early deaths typically result from SIRS leading to multiple organ failure (MOF), while later deaths often stem from infections of pancreatic necrosis and surrounding fluid collections, resulting in sepsis. Over the years, several multifactorial scoring systems have been established and evaluated for their effectiveness and precision in predicting complications, severity, mortality, and the need for intensive care unit (ICU) admission in AP patients. These scoring systems can aid in anticipating the management of AP according to the predicted severity of the disease. Various clinical scoring systems, including Ranson, APACHE II, Glasgow, SIRS, Harmless AP score (HAPS), Japanese Severity Score (JSS), CT Severity Index (CTSI), and Bedside Index of Severity in Acute Pancreatitis (BISAP), have been widely used to assess the potential clinical course of patients. According to the RAC 2012 guidelines, these traditional scoring systems categorize AP severity into mild, moderately severe, and severe. Advances in defining diagnostic criteria for severity and prognosis have significantly shaped treatment approaches. Most of these scoring systems rely on factors such as patient demographics, clinical signs, laboratory results, and imaging studies, assessed at admission or within 48 hours. The majority of the aforementioned scoring systems include the following predictors: age, organ failure, a previous history of chronic disease, temperature, blood pressure, pulse rate, respiratory rate, body mass index, consciousness level, presence of peritonitis, presence of acute renal failure, white blood cell count, blood hematocrit, blood platelet count, blood glucose, blood urea nitrogen, serum creatinine, serum aspartate transaminase, serum lactate dehydrogenase, serum calcium, serum electrolytes, serum bilirubin, plasma albumin, oxygen saturation, pH, base deficit and multiple imaging modalities, mainly CT. However, the reliability of early prognostic evaluations remains uncertain, as patients with identical initial scores can experience markedly different disease trajectories.[25] Currently, no "gold standard" prognostic score exists

for predicting severe AP. The BISAP score is considered one of the most accurate and user-friendly options in clinical settings due to its simplicity and ability to predict severity, mortality, and organ failure, alongside the more complex APACHE II and others.[29] Ranson's criteria, among the earliest predictive models, can be cumbersome in practice, requiring multiple parameters measured at admission and after 48 hours. A meta-analysis indicated that Ranson's score has a poor predictive capability with a high false positive rate.[33] The APACHE II score, utilized upon admission and daily for the first 72 hours, is the most commonly employed severity rating system in ICUs globally. It consists of 12 physiological parameters and adds points for age and chronic conditions. A score below 8 at admission and at 72 hours suggests a mortality rate of under 4%, while scores of 8 or above increase the risk to 11-18%. Changes in the APACHE II score within the first 48 hours are critical for differentiating severity; an increase suggests severe AP, while a decrease indicates mild disease. Despite its advantages, the APACHE II score has limitations, such as difficulty distinguishing between interstitial and necrotizing AP.[34] The SIRS criteria assign points based on thresholds for temperature, respiratory rate, leukocyte count, and heart rate, indicating increased risk for severe disease when present on admission.[36] The Harmless AP score (HAPS) is an easy-to-use scoring system that effectively identifies patients likely to have a mild course of pancreatitis, based on signs of peritonitis, serum creatinine, and hematocrit levels.[37] The JSS, established in Japan in 1990, assesses severity using clinical signs, SIRS, age, various paraclinical parameters, and CT findings, categorized into five degrees.[38] Radiological assessment can also gauge AP severity through the CTSI, which combines Balthazar scores for pancreatic inflammation and necrosis, demonstrating high sensitivity and specificity.[30, 39] The BISAP score, comprising five variables (blood urea nitrogen levels >25 mg/dL, altered mental status, SIRS presence, age >60 years, and pleural effusion) has shown effectiveness in predicting outcomes, with mortality rates ranging from 1% (BISAP=0) to 22% (BISAP=5).[40, 41] Studies comparing various scoring systems, including APACHE II, BISAP, Glasgow, HAPS, JSS, Ranson, and SIRS, showed that these systems generally have moderate accuracy in predicting persistent organ failure. The Glasgow score was identified as the most effective classifier at admission.[42] In another study of 161 patients, significant cutoff values for predicting severe AP were identified for APACHE II, Ranson, BISAP, CTSI, and serum C-reactive protein levels.[43] A meta-analysis concluded that the Balthazar CTSI performed similarly to BISAP, Ranson, and APACHE II for predicting severity but was less accurate for mortality predictions.[44] Serum markers indicating the severity of AP include elevated levels of C-reactive protein (CRP) exceeding 150 mg/L by the third day of symptoms, along with a hematocrit greater than 44% and urea levels above 20 mg/dL. CRP should be measured upon admission and then daily for the first 72 hours. If the CRP is 14.286 nmol/L (150 mg/dL) or higher at admission or within the initial 72 hours, it may indicate AP and is linked to a more severe clinical outcome. Monitoring CRP values within 48 hours of admission can help differentiate between severe and mild cases. The presence of pancreatic necrosis has been correlated with CRP levels exceeding 17,143 nmol/L (180 mg/dL) in the first 72 hours post-onset of symptoms.[45] Additionally, tracking serum procalcitonin daily can non-invasively identify infected necrosis. Other laboratory indicators of severe AP include blood urea nitrogen (BUN) levels above 20 mg/dL (>7.14 mmol/L), increased hematocrit (HCT) beyond 44%, and rising lactate dehydrogenase (LDH) levels. Procalcitonin and IL-8 have demonstrated strong predictive value for assessing the severity of necrotizing AP in the early stages of the disease.[46] Approximately 25% of patients with AP develop severe complications, necessitating ICU admission. Local complications may arise in cases of moderately severe or severe AP, including acute peripancreatic fluid collections (APFCs), pancreatic pseudocysts (PPs), acute necrotic collections (ANCs) and walled-off necrosis (WONs). Roughly 20% of patients may experience recurrent AP, characterized by multiple episodes. About 10% of individuals with a single episode and 36% with recurrent AP may progress

to chronic pancreatitis (CP). The likelihood of developing CP is heightened by factors such as excessive alcohol consumption, smoking, and male gender, with around 5% of CP patients eventually developing pancreatic cancer.[47] Current guidelines suggest monitoring for systemic inflammatory response syndrome or organ failure for at least 48 hours after admission to predict severe disease progression.[28] Recommendations from NICE (National Institute for Health and Care Excellence) and IAP (International Association of Pancreatology) and APA (American Pancreatic Association) emphasize that patients with severe AP should be referred to specialized centers.[28, 48, 49] The majority of patients with mild AP (60-75%) tend to recover without complications, usually resolving symptoms within a few days and requiring 3-6 weeks off work post-discharge, depending on the cause and necessary treatment. Those with moderately severe AP (20-30%) may experience local pancreatic damage, prolonged pain and longer hospital stays, typically needing 6-12 weeks or more off work after discharge. Patients with severe AP often endure extended pain, nutritional deficits and hospitalizations lasting over 4 weeks. If severe AP is complicated by multi-organ dysfunction syndrome (MODS), patients may require critical or high-dependency care, with interventions for infected pancreatic necrosis; mortality rates in this group can reach 50%. Survivors may need to take 12 weeks or more off work and some may never return.[50]

Management of acute pancreatitis

General management

The primary approach to managing AP is supportive care, which involves closely monitoring vital signs, oxygen levels, fluid resuscitation, pain management, and nutrition (Figure 2). For most patients, a target oxygen saturation (SpO2) of 94-98% is recommended. However, those at risk for hypercapnic respiratory failure, such as individuals with chronic obstructive pulmonary disease or significant obesity, may require lower oxygen levels of 88-92%. If oxygen saturation drops below 85%, oxygen should be administered at 15 L/min via a reservoir mask and can be

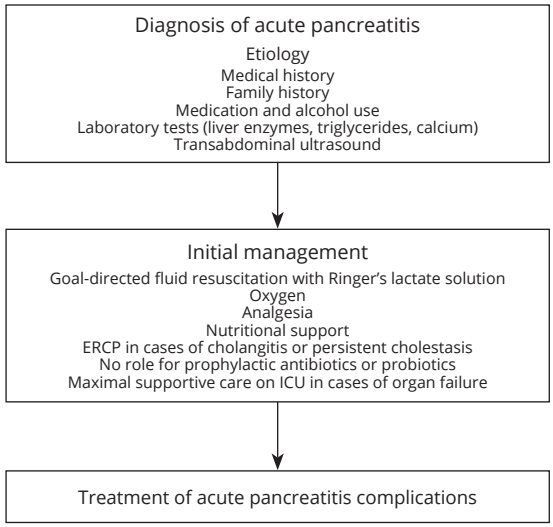

Figure 2.—Initial management of AP.

decreased as the patient's condition stabilizes. Ensuring adequate fluid resuscitation is crucial for correcting fluid deficits, maintaining intravascular volume, and improving organ perfusion. Early fluid resuscitation has been linked to a reduction in the risk of SIRS, ICU admissions, organ failure, and prolonged hospital stays.[4] However, in a randomized trial involving patients with AP, early aggressive fluid resuscitation (consisted of a bolus of 20 ml per kilogram of body weight, followed by 3 ml per kilogram per hour) resulted in a higher incidence of fluid overload without improvement in clinical outcomes.[51] Current guidelines recommend intravenous fluid administration of 5-10 mL/kg/h until a heart rate below 120/min, mean arterial pressure (MAP) between 65 and 85 mmHg, urinary output exceeding 0.5-1.0 mL/kg/h, and hematocrit levels of 35 to 44% are achieved.[28, 33] Some experts advocate for more aggressive hydration strategies (250-500 cc/h with or without boluses) during the first 24 hours to achieve hemodynamic stability. Using Ringer's lactate solution appears to be associated with a lower risk of developing SIRS and reduced C-reactive protein levels compared to normal saline.[30, 52, 53] If the patient remains normovolemic but experiences persistent hypotension, noradrenaline should be the initial vasopressor of choice. While the American Gastroenterological Association (AGA) suggests early goal-directed fluid therapy for managing AP, the supporting

evidence is somewhat limited.[33] Abdominal pain is the predominant symptom in AP patients, necessitating effective analgesic treatment, as unmanaged pain can lead to hemodynamic instability. Various analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), fentanyl, and meperidine, can be utilized, with opioids being the preferred option according to a Cochrane review, which indicates they may reduce the need for additional analgesia.[54] The WSES recommends oxycodone over morphine or fentanyl for non-intubated patients.[29] Although experimental data suggest that opioids might increase phasic contractions of the sphincter of Oddi, leading to elevated bile duct pressure, randomized trials have shown that opioids are generally safe for AP patients and do not cause significant complications.[55] Continuous intravenous opioid infusions may be indicated for severe, persistent pain. NSAIDs can serve as an alternative for patients with uncomplicated disease but carry risks of acute renal injury or peptic ulcers in more severe cases. A multicenter retrospective study indicated that the use of epidural analgesia in ICU patients with AP was linked to a lower 30-day mortality rate compared to those who did not receive it (2% *vs.* 17%).[56] Therefore, epidural analgesia should be considered for patients with severe AP or those requiring long-term intravenous opioids. The WSES guidelines advocate adherence to the latest perioperative acute pain management protocols.[29] The American Society of Anesthesiologists (ASA) recommends a multimodal approach to postoperative analgesia, guided by a validated pain assessment tool.[57] Early feeding, within 72 hours of symptom onset, can enhance outcomes in AP patients. Oral or enteral feeding is associated with reduced pro-inflammatory responses and lower risks of bacterial translocation compared to parenteral nutrition, which poses risks related to catheter placement and infection. In mild AP cases, oral feeding has been shown to shorten hospital stays (from 6 to 4 days) without significant pain recurrence upon refeeding; hence, there is no need to delay enteral feeding until laboratory values normalize or pain subsides. The AGA recommends starting oral feeding within 24 hours if the patient can tolerate it in mild AP cases.[33] The International Association of Pancreatology (IAP) and the American Pancreatic Association (APA) advise initiating oral feeding as abdominal pain decreases and inflammatory markers improve.[28] The American College of Gastroenterology (ACG) suggests starting oral feeding within 48-72 hours unless contraindicated, such as in cases of bowel obstruction or paralytic ileus.[28] During recovery from mild AP, patients are typically fasted initially, and when they can tolerate oral nutrition, they begin with a clear liquid diet to minimize adverse gastrointestinal reactions. The diet is gradually transitioned to soft solids. Discharge from the hospital is contingent upon the effectiveness of the dietary changes and the patient's ability to tolerate solid foods. In severe AP cases, enteral feeding initiated within 24 hours of admission does not offer advantages over oral feeding started at 72 hours if tolerated, given that severe AP could be complicated by ileus, gastric outlet obstruction, and abdominal compartment syndrome, which can hinder enteral nutrition and complicate management decisions.[58, 59] For patients with moderate-to-severe AP, oral feeding may be poorly tolerated due to pain, nausea, or vomiting. Consequently, the NICE recommends initiating enteral feeding within 72 hours.[48] Enteral nutrition is generally considered to be safer and more beneficial than parenteral nutrition, with a lower incidence of septic complications. A meta-analysis of seven randomized controlled trials involving 691 patients found that starting enteral feeding within 24 hours of admission significantly reduced the risk of multiple organ failure (odds ratio [OR] 0.4 [95% CI, 0.2-0.79]; P=0.008) compared to delayed enteral feeding (beyond 24 hours) or parenteral nutrition.[60] Similarly, a Cochrane meta-analysis of eight studies with 348 patients showed that enteral nutrition was associated with lower mortality rates (relative risk [RR] 0.5 [95% CI, 0.28-0.91]), reduced multiple organ failure (RR=0.55 [95% CI, 0.37-0.81]), and fewer systemic infections (RR, 0.39 [95% CI, 0.23-0.65]).[61] Enteral nutrition can be administered *via* nasogastric or nasojejunal tubes. While total parenteral nutrition should be avoided during the course of AP, it can be initiated within 72 hours if enteral feeding fails or is contraindicated. The WSES-guidelines indicate that partial parenteral

nutrition may be considered if enteral routes do not meet nutritional needs.[29] There is currently no specific pharmacological treatment proven effective for AP. Large randomized trials have shown that anti-inflammatory agents (*i.e*. lexipafant), antiproteases (*i.e*. gabexate), and antisecretory agents (*i.e.* octreotide) offer no significant benefits in managing AP.[27] Guidelines from the IAP, APA, WSES, and AGA do not recommend the routine use of intravenous antibiotics for preventing infections in patients with mild, moderately severe, or severe AP, despite the heightened risk of infectious complications in these patients, particularly in the presence of organ failure or local complications.[28, 29, 33] However, if acute pancreatitis is accompanied by infections such as cholangitis or infected WONs, intravenous antibiotics are indicated in cases of infection-related shock, organ dysfunction, or systemic inflammatory response. Common gastrointestinal Gram-negative bacteria, such as *Escherichia coli*, *Proteus*, and *Klebsiella pneumoniae*, are frequently implicated in pancreatic infections, alongside Gram-positive bacteria and fungi like *Candida albicans* and *Candida tropicalis*. Empirical antibiotic therapy should target both aerobic and anaerobic Gram-positive and Gram-negative microorganisms. Antibiotics that are ineffective for AP include penicillins, first-generation cephalosporins, aminoglycosides, and tetracyclines. Effective options against Gram-negative bacteria include imipenem, clindamycin, piperacillin, fluoroquinolones, and metronidazole, all of which have good tissue penetration in cases of infected pancreatic necrosis. Piperacillin/tazobactam is effective against Gram-positive anaerobes. Quinolones, carbapenems, and metronidazole have good pancreatic tissue penetration, but quinolones should be reserved for patients allergic to beta-lactam antibiotics due to widespread resistance. Carbapenems should be limited to critically ill patients because of concerns regarding carbapenem-resistant *Klebsiella pneumoniae*.[47] Compared to other antibiotics, carbapenems significantly reduce mortality, and imipenem has been shown to lower the incidence of infected pancreatic necrosis.[48] Prolonged antibiotic use can increase the risk of fungal infections, although preventive measures against fungal infection are not recommended.[27]

Cholecystectomy

The optimal timing and method for treating biliary stones in cases of acute biliary pancreatitis remain debated. This approach does not significantly increase the risk of conversion to open cholecystectomy or complications, nor does it prolong procedural time.[30] The PONCHO trial demonstrated the advantages of performing cholecystectomy during the same admission compared to delaying it (25-30 days), resulting in lower readmission rates for gallstone-related complications and reduced mortality.[62] In cases of moderate-to-severe disease cholecystectomy should be delayed until local or systemic complications resolve, as it is associated with increased postoperative mortality and morbidity.[63] Early cholecystectomy in patients with fluid collections may lead to higher rates of infectious complications, so it should be postponed until these collections have stabilized or subsided, and acute inflammation has resolved.[64] For patients experiencing an inflammatory response, it is recommended to delay cholecystectomy for at least six weeks until the inflammation has regressed.[64] The optimal timing of cholecystectomy after necrotizing biliary pancreatitis, in the absence of peripancreatic collections, is within 8 weeks after discharge.[65] For elderly patients who cannot tolerate surgery, endoscopic sphincterotomy (EST) offers a temporary solution to reduce the risk of recurrent biliary pancreatitis, with definitive cholecystectomy performed once the patient's condition has improved.

Bile duct stones and ERCP

A meta-analysis found that routine ERCP in biliary AP is not beneficial.[54] The indications for ERCP in acute gallstone pancreatitis include acute gallstone pancreatitis with cholangitis or common bile duct obstruction.[66] A multicenter randomised controlled trial showed that in patients with severe acute biliary pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not decrease the composite endpoint of major complications or mortality compared with conservative treatment.[67] In patients with severe acute gallstone pancreatitis with associated cholangitis, early ERCP is associated with decreased mortality and fewer complications, and similarly, it helps to reduce local complications in cases of pancre-

atitis with biliary obstruction.[29] However, WSES guidelines suggest that urgent ERCP should be performed within 24 hours for patients with acute biliary pancreatitis who also have cholangitis, as delays can increase mortality risk.[39, 40] However, the AGA advises against performing ERCP within this timeframe, recommending instead an initial period of resuscitation and observation.[33] For patients with acute biliary pancreatitis and common bile duct (CBD) obstruction, early ERCP within 72 hours is recommended.[28, 29, 33] The International Association of Pancreatology (IAP) emphasizes the importance of confirming CBD obstruction through MRCP or EUS before proceeding with ERCP to avoid unnecessary interventions. While EUS is more effective at detecting small stones under 5 mm, it is also more invasive and less widely available.[30] In case of resolution of CBD obstruction or if CBD obstruction is absent, ERCP is not indicated. ERCP serves as both a diagnostic and therapeutic procedure for managing biliary disorders, but post-ERCP pancreatitis (PEP) is a common complication that can lead to significant morbidity and occasional mortality. In cases of PEP, management should include aggressive intravenous hydration, pain control, and early enteral nutrition.

Complications of acute pancreatitis

AP may be associated with local and/or systemic complications. Local complications of AP include pancreatic necrosis, different pancreatic or peripancreatic fluid and solid collections (APFCs, PPs, ANCs and WONs), gastric outlet dysfunction, intestinal ischemia, splenic or portal vein thrombosis, disruption or disconnection of the main pancreatic duct, involvement of contiguous organs due to necrotizing pancreatitis, colonic necrosis, abdominal compartment syndrome and pseudoaneurysm. Systemic complications of AP often present as organ failure, which can be temporary in cases of moderately severe AP or long-lasting in severe AP cases.

Local complications of acute pancreatitis

Infected pancreatic necrosis

Approximately 5% to 10% of patients with severe AP develop necrosis. Among those with acute necrotic collections, about 6% become infected, 41% resolve, and 38% develop WONs after four weeks.[31] Most patients with sterile pancreatic or peripancreatic necrosis can be managed conservatively, regardless of the size or extent of the collections. However, drainage of sterile necrosis can risk introducing infection, leading to further interventions and related complications. Surgical intervention should only be considered for a small group of patients with persistent symptoms such as abdominal pain, gastric outlet obstruction, jaundice, or failure to thrive, at least 4 to 8 weeks after the onset of the disease, as most collections typically resolve over time.[28] Infected pancreatic necrosis is a significant negative prognostic factor and the primary cause of morbidity and mortality in severe AP. Diagnosing infected pancreatic necrosis poses challenges, as its clinical presentation often overlaps with other infectious complications or the inflammatory responses of AP. About 50% of patients can be diagnosed with infected necrosis through the detection of gas in pancreatic collections on CECT. In the remaining cases, clinical signs of infection may suffice for diagnosing secondary infections of pancreatic or peripancreatic necrosis. While some experts suggest fine needle aspiration for confirming infection in ambiguous cases, this method is associated with a false-negative rate of 12-25%.[31] For patients with clinically confirmed or highly suspected infected necrosis, surgical intervention is critical and should adhere to the "3D" principles: delay, drain, and debride. Recent studies have suggested that antibiotics alone can sometimes resolve the infection and, in select cases, avoid the need for surgery[68] (Figure 3). Traditional open abdominal debridement has a reported complication rate of 34-95% and a mortality rate of 5.6-39%.[69] Over the last decade, minimally invasive techniques have largely replaced traditional open surgery for infected necrotizing pancreatitis. The treatment approach for infected pancreatic necrosis has evolved to be more varied, depending on the patient's overall health, the extent of necrosis, and other clinical factors. The "step-up" approach has become the gold standard for managing infected pancreatic or peripancreatic necrosis, offering a less invasive alternative to surgical necrosectomy

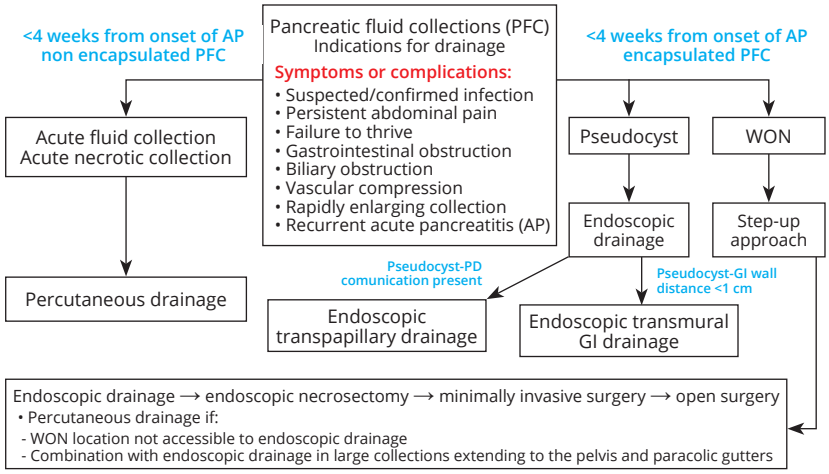

Figure 3.—Management of pancreatic fluid collections.

(Figure 4). This approach focuses on controlling SIRS rather than completely removing necrotic tissue, which helps lower postoperative complications and mortality rates. Studies have shown that the step-up method significantly reduces morbidity and mortality compared to traditional surgical options, provided both approaches are technically feasible.[25] Current consensus indicates that surgery is warranted for clinically unstable patients with infected necrosis. The step-up strategy begins with monitoring and conservative care, followed by options such as percutaneous catheter drainage or endoscopic transluminal drainage and minimally invasive necrosectomy (*e.g.*, laparoscopic necrosectomy or videoscopic-assisted retroperitoneal debridement) when clinically necessary. In stable AP patients with infected necrotizing pancreatitis, the initial step involves a 30-day course of broad-spectrum antibiotics, with some patients managing well on supportive care alone without further invasive procedures. The AGA recommends using carbapenems, quinolones, metronidazole, or higher-generation cephalosporins.[33] Guidelines from the WSES, the IAP, and the AGA suggest postponing invasive interventions, including catheter drainage placement, for several weeks to allow for the development of WONs, while ensuring close monitoring to promptly identify patients who are not improving with conservative management.[28, 29, 33] For necrotic collections with a well-defined wall and liquefied contents, the choice and method of drainage (whether endoscopic, radiologic, or surgical) can then be considered. In patients with AP who experience clinical deterioration after starting empirical antibiotic therapy, fine needle aspiration (FNA) samples can be valuable for identifying infections and guiding

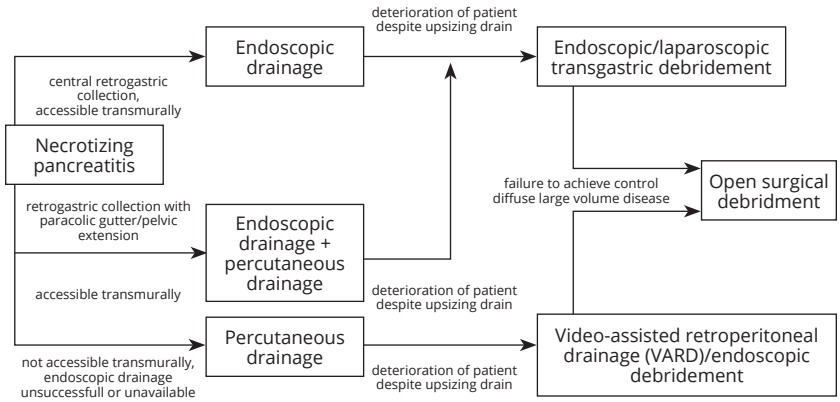

Figure 4.—Step-up algorithm for management of necrotizing pancreatitis.

antibiotic adjustments. If no clinical improvement is observed within 48 to 72 hours following initial drainage, a second catheter drainage or an expanded drainage channel should be created. Should the patient still show no signs of improvement after an additional 48 to 72 hours, minimally invasive necrosectomy should be considered. Transperitoneal laparoscopy is generally discouraged due to technical challenges and the risk of contaminating the peritoneal cavity. Video-assisted retroperitoneal debridement (VARD) involves endoscopic necrosectomy using a zero-degree videoscope inserted through a dilated percutaneous drain tract. A 5 cm subcostal incision is made in the left flank, and necrotic tissue is initially mobilized with grasping forceps before the videoscope is inserted to remove residual necrosis with laparoscopic grasping tools. If these methods are ineffective, open necrosectomy may be necessary. However, a recent randomized controlled trial indicated that open necrosectomy is associated with a high complication and mortality rate (69%).[69] The notion that urgent surgery is essential for all patients with infected necrosis has been challenged.[68] Laparotomy should be delayed as long as possible or avoided to reduce morbidity and mortality. Surgery is ideally postponed for 4 to 6 weeks following the onset of infected pancreatic necrosis, allowing the necrotic tissue to liquefy and form an envelope that clearly delineates it from surrounding tissues, thus preserving more healthy pancreatic tissue. Early surgical intervention can help lower the risk of complications such as intestinal fistula, bleeding, and infections. Necrosectomy should only be performed before 4 weeks if there are strong indications and an organized collection. The fundamental principle of open pancreatic necrosectomy involves exposing the necrotic area, typically after transecting the gastrocolic and duodenocolic ligaments, followed by blunt dissection and debridement of necrotic tissue. The management of the necrotic cavity can take several forms: 1) open packing, where the cavity is packed and the patient returns for repeat procedures (usually every 48 hours) until the necrotic process resolves (mortality rates range from 12% to 49% with infected necrosis); 2) planned relaparotomies, where the patient is scheduled for re-laparotomy after initial necrosectomy and lavage (mortality rates of 17% to 25%); 3) closed continuous lavage, involving the placement of multiple large double-lumen tubes in the necrotic area for suction drainage and venting, combined with high-volume continuous lavage immediately post-surgery (mortality rates from 12% to 49%); and d) closed packing, where packing is combined with the use of Penrose and closed-suction drains (mortality rate of 6%). The IPA and APA guidelines support both percutaneous and endoscopic approaches.[28] The NICE recommends beginning with an endoscopic approach if anatomically feasible, reserving percutaneous methods for situations where endoscopic drainage is not possible.[48] The WSES advocates for percutaneous drainage as the first-line treatment.[29] A systematic review on the use of percutaneous catheter drainage as the primary treatment for necrotizing pancreatitis found that 56% of patients with infected pancreatic necrosis did not require surgery after undergoing percutaneous drainage. This method not only provides rapid and effective source control but also allows for the possibility of delaying surgical intervention until a more favorable time.[70] Additionally, percutaneous drainage facilitates bedside lavage, and the catheter tract can serve as a pathway for subsequent VARD. However, a significant drawback of percutaneous drainage is the higher incidence of pancreatic fistulae compared to endoscopic approaches (32% *vs*. 2%).[70] There is ongoing debate regarding the best strategy if percutaneous drainage fails to resolve the infection. Management options include open surgery, minimally invasive surgery, endoscopic surgery, or a combination of these. The American Gastroenterological Association (AGA) updated its guidelines in 2020, advocating for a flexible approach that takes into account the patient's physiology, disease pattern, the multidisciplinary team's expertise, and available resources, with a preference for endoscopic drainage when feasible.[33] The PANTER trial (2010) demonstrated that the minimally invasive step-up approach, comprising initial percutaneous catheter drainage followed by VARD if necessary, significantly reduced the rates of organ failure (12% *vs.* 40%), incisional hernia (7% *vs*. 24%), and diabetes

(16% *vs*. 38%) while lowering mortality rates in patients with infected pancreatic necrosis compared to traditional open necrosectomy.[69] An eight-year follow-up of PANTER participants revealed that the step-up approach was associated with lower rates of exocrine (29% *vs*. 56%) and endocrine dysfunction (40% *vs*. 64%) compared to open surgery. However, there were no significant differences between the two groups regarding rates of redrainage, debridement, recurrent acute pancreatitis, chronic pancreatitis, pain scores, hospital costs, or quality of life. Although the step-up approach resulted in more interventions, it did not increase risks compared to open surgery. The POINTER trial (2021) further indicated that a postponed-drainage strategy led to fewer invasive interventions compared to an immediate-drainage strategy, without raising complication rates.[71] Therefore, percutaneous drainage should ideally be postponed for about four weeks after disease onset.[72] The PENGUIN trial (2012) showed that endoscopic drainage followed by necrosectomy, if needed, resulted in a reduced post-procedural pro-inflammatory response and improved clinical outcomes compared to percutaneous drainage followed by VARD or laparotomy when necessary.[73] The TENSION trial (2021) and the ExTENSION trial (2022) reported no significant superiority of the endoscopic step-up approach over the surgical step-up approach in reducing major complications or mortality, although the endoscopic group experienced fewer pancreatic fistulas and shorter hospital stays.[74, 75] The MISER trial (2019) indicated that an endoscopic transluminal approach for infected pancreatic necrosis significantly lowered major complications, reduced costs, and improved quality of life compared to minimally invasive surgery; however, the endoscopic step-up may not be suitable for all acute pancreatitis patients, and surgical step-up may be preferable for managing bilateral paracolic sulci and pelvic cavity issues. If neither percutaneous nor endoscopic interventions improve the patient's condition, surgical options should be considered.[76]

Pancreatic fluid collections

PFCs frequently arise as complications in cases of moderate to severe AP, particularly in interstitial and necrotizing forms. A significant number of PFCs, up to 80%, can be asymptomatic and may resolve on their own without any treatment; however, intervention is necessary if they become symptomatic or develop complications. More than 70% of PPs can resolve without drainage, while up to 50% of WONs, even if infected, may improve with conservative management.[33, 77, 78] The management of PFCs has advanced significantly in recent years, shifting from open surgical techniques to minimally invasive procedures. Currently, a step-up approach is considered the standard of care for treating infected pancreatic necrosis as well. Interventions may involve drainage, lavage, fragmentation, debridement, or excision, depending on the type of fluid collection. Drainage methods include percutaneous catheter drainage, endoscopic drainage and surgical debridement. Recommendations for drainage arise in cases of persistent abdominal pain, gastrointestinal or biliary obstruction due to large collections, bleeding, rapidly enlarging fluid collections, recurrent episodes of pancreatitis, abdominal compartment syndrome, and particularly in instances of suspected or confirmed infection, especially in the context of WONs.[33, 78] It is thought that patients with pseudocysts larger than 6 cm are more likely to experience clinical symptoms. Collections that do not necessitate drainage include asymptomatic WONs, non-infected PPs, and abdominal pseudocysts that drain spontaneously via gastrointestinal fistulas. Performing any intervention on PFCs in acutely ill patients during the early phase of AP is linked to increased morbidity and mortality, primarily due to SIRS and heightened hemorrhage risk. Current guidelines advise postponing interventions, whether percutaneous, endoscopic, or surgical, for at least 3 to 4 weeks after the onset of the disease to minimize these risks and allow for the encapsulation of fluid collections. Surgical drainage techniques, such as cystogastrostomy or cystoduodenostomy, involve creating a passage between the PFC and the stomach or small intestine, achieving excellent resolution rates (91-97%).[79] According to the AGA Clinical Practice Update 2020, both percutaneous and endoscopic transmural interventions are suitable first-line treatments for

WONs and organized PFCs. Percutaneous drainage is particularly recommended for patients with infected or symptomatic ANCs when they are too unwell for endoscopic or surgical options. Within the first four weeks, percutaneous drainage is the standard approach for symptomatic or necrotic collections and can be employed alongside endoscopic methods or as a standalone treatment for collections with significant depth. This method is especially advantageous for fragile patients with severe comorbidities or immature infected fluid collections who are not candidates for more invasive interventions. It is particularly effective for PFCs located in the paracolic gutters or pelvis, which are difficult to access via endoscopy. However, percutaneous drainage does have limitations, including potential challenges in securing a safe access route, risks of hemorrhage and pancreatic fistulas, and the likelihood of requiring additional interventions, which can lead to prolonged hospital stays. Percutaneous drainage of PFCs can be performed using US or CT guidance. CT guidance is generally preferred for lesser sac collections because it helps avoid the bowel and facilitates easier retroperitoneal access. Ultrasound guidance is suitable for larger, superficial collections or in emergency situations, such as when a patient is septic and needs immediate drainage. When selecting access routes for percutaneous catheter drainage, care is taken to avoid the intestine to prevent enteric leaks or contamination of sterile collections, as well as to avoid major blood vessels. The retroperitoneal route through the flank is considered ideal, as it bypasses the intestine, minimizes the risk of infection spreading to the peritoneal cavity, and allows for potential future minimally invasive surgeries. The transperitoneal route is the second choice when retroperitoneal access is not feasible, especially for collections located anteriorly near the pancreatic head and proximal body. In cases where there is no free access to the lesser sac, a transgastric approach may be utilized, which is relatively safe due to the bacteria-free, acidic contents of the stomach. The transhepatic route is rarely used and should generally be avoided unless no other options are available.[80] Drainage can be achieved using either the Seldinger technique or the trocar technique. The Seldinger method is more suited for deep collections but is more time-consuming due to its multi-step process. The trocar technique, on the other hand, is better for large, superficial collections, though it may be more painful.[81] The initial size of the catheter is crucial for the success of percutaneous drainage, yet this factor is often underexplored in the literature. Success rates for percutaneous drainage range from 14% to 86%, with relatively low morbidity and mortality; diligent care, including proper cleaning and frequent irrigation of drains, can further enhance outcomes.[82, 83] PFCs typically form in the spaces between anatomical structures like the stomach and duodenum. This proximity has led to the development of endoscopic drainage techniques, which tend to have fewer complications. Endoscopic drainage and necrosectomy have evolved over the past two decades into preferred treatment modalities, particularly with advancements in techniques and equipment, such as novel stents. The two main procedures for drainage are transgastric and transduodenal, and the choice between them often hinges on the anatomical relationship between the WONs and the gastrointestinal tract. Compared to percutaneous drainage, endoscopic techniques generally offer better tolerability and reduce the risk of pancreaticocutaneous fistulas. According to ESGE guidelines, endoscopic or percutaneous drainage is recommended as the first line of intervention for infected WONs. If there is no improvement after endoscopic transmural drainage, endoscopic necrosectomy or minimally invasive surgery is preferred over open surgery for subsequent management.[78] For endoscopic drainage consideration, a PFC should typically be at least 3 cm in size, although there are no strict size guidelines. Additional criteria include an international normalized ratio (INR) of less than 1.5, platelet counts above 50,000/μL, and the cessation of direct oral anticoagulants for at least 48 hours.[84] A mature wall around PPs or WONs is critical, as performing endoscopic cystogastrostomy in its absence may lead to perforation. It is advised that the target cyst or WONs is located within 10 mm of the gastrointestinal lumen, as assessed by EUS, to ensure technical success and allow for the evaluation of pseudoaneurysms and nearby vascular

structures prior to intervention.[85, 86] The contents of PPs are typically fluid, so one to two 7-10 Fr pigtail stents are usually adequate for drainage, unless multiple pseudocysts necessitate additional stenting. In contrast, WONs often require multiple stents due to the presence of debris, or a large-caliber fully covered metal stent or lumen-apposing metal stents (LAMS). Some medical centers utilize a hybrid technique for managing WONs that combines the placement of a large-caliber percutaneous drain for irrigation with the creation of an endoscopic cystogastrostomy to facilitate egress for lavage. Endoscopic drainage of PPs can be approached in two ways: transpapillary or transmural. Transpapillary drainage via ERCP is reserved for small collections that connect with the main pancreatic duct.[87] This method allows for continuous drainage of pancreatic fluid and helps resolve any ductal disruptions causing the pseudocyst. However, most PPs and all WONs are drained using a transmural approach, as combining both transpapillary and transmural drainage does not provide additional benefits.[88] Endoscopic transmural drainage can be conducted using conventional endoscopic guidance or EUS. Previously, conventional drainage involved identifying a bulge in the gastrointestinal wall, puncturing it for aspiration, and injecting contrast to localize the PFC before placing a guidewire. With EUS, the characteristics of the fluid collection, such as size, wall thickness, and nearby vasculature, can be thoroughly assessed. Using a linear array echoendoscope, the collection is localized from the stomach or small intestine, and color flow Doppler imaging is employed to visualize regional vasculature before puncture. A 19-gauge fine-needle aspiration (FNA) needle is used for puncturing the gastrointestinal wall under direct EUS visualization, allowing fluid aspiration for culture. A guidewire is then threaded into the collection, followed by dilation and stent placement. If necessary, electrocautery devices, such as a needle knife or cytostome, can create a fistula, which is subsequently dilated to 6-8 mm to facilitate stent insertion. Stents can be either plastic or metallic, with metallic stents generally offering better drainage outcomes due to their larger lumens, which also enable endoscopic necrosectomy. Due to the requirement for multiple plastic stents across the fistula to enhance drainage and prevent occlusion complications, fully covered self-expandable metal stents (FCSEMSs) have gained popularity. These stents lower the risk of leakage between the cyst and the gastrointestinal lumen, decrease the likelihood of bleeding by providing a tamponade effect, and shorten procedure times.[89] The larger lumen diameter (6-10 mm) of FCSEMSs enhances drainage and reduces stent occlusions, recurrences, and secondary infections. However, because FCSEMSs are not anchored and were originally designed for bile duct drainage, they carry a higher risk of migration, often necessitating the placement of a coaxial double-pigtail plastic stent for stabilization. Newer stent designs, such as lumen-apposing metal stents (LAMS) and bi-flanged metal stents, have further improved prevention of migration and outperform earlier metal stent models. Examples include the AXIOS stent, Nagi stent, and Niti-S SPAXUS stent. The AXIOS stent, for instance, features a nitinol braided structure with double-walled flanges in a dumbbell configuration, designed to reduce migration and minimize the risks of perforation, leakage, and stent erosion.[90] Potential complications from these procedures include bleeding from the fistula tract or within the PFC due to erosion of large vessels, perforation (especially if the wall is poorly defined or if the distance to the intestinal lumen exceeds 1 cm) stent migration into the PFC or gastrointestinal lumen (which is more common with biliary stents), and stent occlusion leading to secondary infection of the PFC, which may require endoscopic revision to clear the blockage. Endoscopic necrosectomy involves manually removing necrotic tissue from WONs using a gastroscope for mechanical clearance. The scope is inserted into the collection, allowing for irrigation and suction to clear debris. Larger pieces of necrotic material can be extracted using various tools, such as forceps or polypectomy snares, while lavage with diluted hydrogen peroxide may facilitate debridement. Nasocystic drains can be utilized as adjuncts, with intermittent saline irrigation to reduce the need for repeated endoscopic debridement. Currently, necrosectomy is generally reserved for WONs that do not im-

prove after appropriate drainage, with predictive factors for the need for necrosectomy including large size and significant solid debris.[91] Sessions for necrosectomy can occur every 2-5 days until most non-adherent necrotic material is removed and/or there is clinical improvement.[92] The timing for stent removal is assessed 1-2 months post-initial placement, during which repeat imaging is conducted to evaluate the resolution of the fluid collection.

Disconnected main pancreatic duct (DPD) syndrome

Disconnected main pancreatic duct (DPD) refers to a circumferential interruption of the main pancreatic duct (MPD) and is often associated with severe necrotizing pancreatitis, particularly with central pancreatic necrosis. The prevalence of DPD syndrome in patients experiencing necrotizing pancreatitis is estimated to be between 30% and 50%.[93, 94] During necrotizing pancreatitis, inflammation can lead to the leakage of pancreatic secretions into both pancreatic and peripancreatic tissues, resulting in sterile pancreatic necrosis. This process can disrupt the pancreatic duct, breaking the continuity between the duct in the left pancreas and the gastrointestinal tract. In cases where the duct loses its connection to viable pancreatic tissue, it fails to drain into the duodenum, leading to a persistent pancreatic fistula and a high likelihood of forming peripancreatic collections. The pathological consequences of this drainage persist until it is surgically redirected, the disconnected pancreatic segment is resected, or the segment undergoes atrophy. There are three recognized types of DPD syndrome: 1) concurrent DPD, where necrosis affects the neck and body of the pancreas but the tail remains perfused; 2) delayed DPD, characterized by peripancreatic collections or WONs in the middle of the gland while the left pancreatic remnant remains perfused; and 3) DPD associated with chronic pancreatitis, where a stricture or stone obstructs the proximal duct, leading to atrophy of the distal segment and resulting in the formation of pseudocysts. The clinical manifestations of DPD syndrome can vary widely and may include recurrent peripancreatic fluid collections, persistent external pancreatic fistulas, pancreatic ascites, pleural effusions, and/or recurrent episodes of acute or chronic pancreatitis in the upstream portion of the gland. Diagnosis of DPD syndrome typically involves imaging techniques such as CECT, MRI, MRCP, and EUS. Initial management of pancreatic necrosis causing DPD syndrome may include percutaneous, endoscopic, or minimally invasive surgical methods as temporary solutions.[95] A commonly accepted approach is endoscopic transluminal drainage of associated fluid collections using double-pigtail plastic stents, which can be left in place indefinitely to facilitate internal drainage to the stomach. While combined endoscopic drainage and routine stenting of the pancreatic duct are not recommended for duct disconnection, transpapillary bridging may be an option for patients with duct disruption.[78] For local duct disruption, a stent can be inserted via ERCP to promote healing. In cases where a drain tract pseudocyst recurs due to a distal stricture, Roux-en-Y pseudocyst-enterostomy is often the best management strategy. Ultimately, the standard treatment for DPD syndrome is the surgical resection of the disconnected pancreatic segment, with elective distal pancreatectomy being the definitive approach for most patients.[96]

Pancreatic fistula

Pancreatic fistulas arise from the autodigestion or necrosis of the pancreas, leading to a persistent disruption of the pancreatic duct. When the duct is disrupted, the connection between it and healthy pancreatic tissue is lost, resulting in pancreatic secretions no longer flowing into the duodenum but instead accumulating in surrounding areas, which can lead to the formation of pancreatic complications. These secretions may also reach distant locations, potentially causing pancreatic ascites, pleural effusions, or even distant pancreatic complications and pancreatocutaneous fistulas. Additionally, pancreatic fistulas can result from percutaneous catheter drainage. They are classified into two categories: 1) internal, where the pancreatic duct connects with the peritoneal or pleural cavity or another hollow organ, and 2) external, where it communicates with the skin. The treatment approach for pancreatic fistulas depends on the location of the duct disrup-

tion and whether there is downstream ductal obstruction or DPD syndrome. In the initial stages, management is typically conservative, involving total parenteral nutrition and the use of the pancreatic secretory inhibitor octreotide. If conservative measures fail, further intervention, including surgery, may be necessary, although surgical procedures can be technically difficult and may lead to significant complications.

Colonic and enteric fistula

Ischemia, necrosis, and hemorrhage in the enteric and colonic regions during severe AP are primarily due to the leakage of pancreatic enzymes and the necrosis surrounding the pancreas. When an enteric or colonic fistula is identified, segmental intestinal resection becomes essential. Colonic fistulas occur in approximately 17-19% of patients and are linked to a higher risk of mortality.[43] About 47% of these cases can be managed non-surgically through percutaneous drainage. In a study involving 132 patients with colonic fistulas, the mortality rate for those needing surgical intervention was notably higher at 37%, compared to 19% for those treated with percutaneous drainage.[97]

Hemorrhage

Upper gastrointestinal bleeding is a frequent occurrence in AP and is typically attributed to stress ulcers, peptic ulcer disease, or hemorrhagic gastroduodenitis. While massive hemorrhage is uncommon, it can happen, particularly into the gastrointestinal tract, abdominal cavity, or pancreatic duct. Complications such as pancreatic fistula and necrosis can damage blood vessels in the vicinity, leading to significant bleeding in 15-18% of cases, often due to the rupture or formation of a pseudoaneurysm, which carries a mortality rate of 34-52%.[98] The splenic artery is most commonly affected, followed by the pancreaticoduodenal and gastroduodenal arteries. Pseudoaneurysm should be suspected in patients experiencing recurrent gastrointestinal bleeding, a growing pulsatile abdominal mass, or increasing abdominal pain and bloating. Unfortunately, rupture of these aneurysms typically results in severe, life-threatening hemorrhage. Diagnosis can be confirmed through CT angiography or angiography. For hemodynamically stable patients, CT angiography is recommended. Active arterial bleeding cases should be treated with emergency embolization, while those with venous bleeding may first be managed conservatively, focusing on correcting coagulopathy and administering octreotide. If these methods fail, surgical intervention may be necessary for hemostasis. Conversely, hemodynamically unstable patients require immediate surgical hemostasis, which might involve packing to gain control before proceeding with embolization. A review of 200 cases found that endovascular management was successful in 75% of instances, with first-line endovascular therapy associated with a lower mortality rate compared to primary surgical approaches.[99]

Venous thrombosis

Venous thrombosis is one complication of AP which can give rise to thrombosis of the peripheral vasculature in the form of deep vein thrombosis, pulmonary embolism, and splanchnic vein thrombosis. The prevalence of these complications increases with the severity of the disease and adds to the adverse outcomes profile. Nowadays there is no consensus guideline for anticoagulation management in this setting. Superior mesenteric vein or portal vein thrombosis is often managed with six months of therapeutic low-molecular-weight heparin with or without conversion to oral anticoagulation as appropriate, while isolated splenic vein thrombosis is treated with prophylactic low-molecular-weight heparin. However, an observational study failed to show benefit of anticoagulation in rates of recanalization or mortality.[100]

Abdominal compartment syndrome

Abdominal compartment syndrome (ACS) is characterized by sustained intra-abdominal pressure exceeding 20 mmHg, accompanied by new organ dysfunction. In cases of severe AP, initial management of ACS should be conservative, focusing on stopping unnecessary fluid infusions, using diuretics (or ultrafiltration if needed), reducing gastrointestinal volume through methods such as nasogastric drainage and enemas, promoting abdominal wall relaxation, and draining

ascites. If nonoperative measures fail, surgical decompression may be necessary, potentially utilizing an open abdomen approach to manage ACS. During a decompressive laparotomy, care should be taken to preserve the retroperitoneal cavity and lesser omental sac to minimize the risk of infection in the peripancreatic and pancreatic necrosis areas. Re-exploration of the open abdomen should occur no later than 24-48 hours after the initial and any subsequent surgeries, with the interval between operations decreasing as patient condition worsens and hemodynamic instability increases. Once ongoing resuscitation is no longer required, source control has been adequately established, intestinal viability is confirmed, no further surgical exploration is needed, and there are no concerns about developing ACS, the goal should be early fascial and/or definitive closure of the abdomen.[29]

Conclusions

AP is a prevalent inflammatory condition of the pancreas with a complex pathogenesis that can escalate to a severe form, characterized by a high mortality rate and limited effective control. It is a common cause for hospital admissions, requiring a multifaceted approach to both diagnosis and management. Once diagnosed, clinical efforts should focus on identifying the underlying causes while managing the condition and anticipating potential complications, which can be facilitated by utilizing various severity scoring systems. The initial management of AP is primarily supportive and applies to both mild and severe cases, while later treatment addresses complications arising from severe AP. Although there is no consensus on the optimal type and regimen of fluids for resuscitation, goal-directed fluid therapy has been associated with improved outcomes. Early enteral nutrition is beneficial as it helps modulate the inflammatory response and reduces the risk of infectious complications. Antibiotics should be used cautiously, as prophylactic use has not demonstrated benefits in preventing infections related to AP. Patients with mild acute gallstone pancreatitis are advised to undergo laparoscopic cholecystectomy during their initial admission, while those with severe cases presenting with cholangitis or choledocholithiasis should receive ERCP. For patients with mild acute gallstone pancreatitis and concurrent choledocholithiasis, a single-stage laparoscopic approach for both cholecystectomy and bile duct exploration is beneficial, depending on local expertise. The treatment paradigm for severe AP complications has shifted from early surgical intervention to a minimally invasive step-up approach as the standard. However, due to the complexity of AP and its various outcomes, predicting its clinical trajectory remains challenging. This complexity highlights the necessity for a thorough management strategy encompassing prevention, diagnosis, and treatment. Consequently, a coordinated multidisciplinary effort is essential to mitigate the impact of AP and enhance patients' quality of life. Further research, particularly randomized trials and prospective collaborative studies, is needed to deepen our understanding of the disease's pathophysiology and to address the diagnostic and therapeutic challenges, ultimately improving the management of severe forms of AP.

References

1. Szatmary P, Grammatikopoulos T, Cai W, Huang W, Mukherjee R, Halloran C, *et al*. Acute Pancreatitis: diagnosis and Treatment. Drugs 2022;82:1251–76.

2. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol 2019;16:175–84.

3. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, *et al.*; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.

4. Garber A, Frakes C, Arora Z, Chahal P. Mechanisms and Management of Acute Pancreatitis. Gastroenterol Res Pract 2018;2018:6218798.

5. Klöppel G. Acute pancreatitis. Semin Diagn Pathol 2004;21:221–6.

6. Heckler M, Hackert T, Hu K, Halloran CM, Büchler MW, Neoptolemos JP. Severe acute pancreatitis: surgical indications and treatment. Langenbecks Arch Surg 2021;406:521–35.

7. Whitcomb DC; North American Pancreatitis Study Group. Pancreatitis: TIGAR-O version 2 risk/etiology checklist with topic reviews, updates, and use primers. Clin Transl Gastroenterol 2019;10:e00027.

8. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–61.

9. Mederos MA, Reber HA, Girgis MD. Acute Pancreatitis: A Review. JAMA 2021;325:382–90.

10. Forsmark CE, Vege SS, Wilcox CM. Acute Pancreatitis. N Engl J Med 2016;375:1972–81.

11. Krishna SG, Kamboj AK, Hart PA, Hinton A, Conwell DL. The changing epidemiology of acute pancreatitis hospitalizations. Pancreas 2017;46:482–8.

12. Sellers ZM, Barakat MT, Abu-El-Haija M. A Practical Approach to Management of Acute Pancreatitis: Similarities and Dissimilarities of Disease in Children and Adults. J Clin Med 2021;10:2545.

13. Rey C, Conde D, Girón F, Ayala D, Gonzalez J, Melo D, *et al.* Trans-gastric and trans-abdominal percutaneous drainage of acute peripancreatic fluid infected collections: A retrospective analysis. Ann Med Surg (Lond) 2022;79:104080.

14. Jinno N, Hori Y, Naitoh I, Miyabe K, Yoshida M, Natsume M, *et al.* Predictive factors for the mortality of acute pancreatitis on admission. PLoS One 2019;14:e0221468.

15. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, *et al.* Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. Gastroenterology 2019;156:254–272.e11.

16. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, *et al.* Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol 2016;1:45–55.

17. Sellers ZM, MacIsaac D, Yu H, Dehghan M, Zhang KY, Bensen R, *et al.* Nationwide Trends in Acute and Chronic Pancreatitis Among Privately Insured Children and Non-Elderly Adults in the United States, 2007-2014. Gastroenterology 2018;155:469–478.e1.

18. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology 2017;17:155–65.

19. Hamada S, Masamune A, Kikuta K, Hirota M, Tsuji I, Shimosegawa T; Research Committee of Intractable Diseases of the Pancreas. Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas 2014;43:1244–8.

20. Toouli J, Brooke-Smith M, Bassi C, Carr-Locke D, Telford J, Freeny P, *et al.*; Working Party of the Program Commitee of the Bangkok World Congress of Gastroenterology 2002. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2002;17(Suppl):S15–39.

21. Husic-Selimovic A, Bijedic N, Sofic A, Selimagic A, Vanis N, Jahic R, *et al.* Prediction of Surgical Treatment in Acute Pancreatitis Using Biochemical and Clinical Parameters. Med Arh 2023;77:29–33.

22. Hu JX, Zhao CF, Wang SL, Tu XY, Huang WB, Chen JN, *et al.* Acute pancreatitis: A review of diagnosis, severity prediction and prognosis assessment from imaging technology, scoring system and artificial intelligence. World J Gastroenterol 2023;29:5268–91.

23. Gumaste VV, Roditis N, Mehta D, Dave PB. Serum lipase levels in nonpancreatic abdominal pain versus acute pancreatitis. Am J Gastroenterol 1993;88:2051–5.

24. Hameed AM, Lam VW, Pleass HC. Significant elevations of serum lipase not caused by pancreatitis: a systematic review. HPB (Oxford) 2015;17:99–112.

25. Zerem E, Kurtcehajic A, Kunosić S, Zerem Malkočević D, Zerem O. Current trends in acute pancreatitis: diagnostic and therapeutic challenges. World J Gastroenterol 2023;29:2747–63.

26. Shah AP, Mourad MM, Bramhall SR. Acute pancreatitis: current perspectives on diagnosis and management. J Inflamm Res 2018;11:77–85.

27. Walkowska J, Zielinska N, Tubbs RS, Podgórski M, Dłubek-Ruxer J, Olewnik Ł. Diagnosis and Treatment of Acute Pancreatitis. Diagnostics (Basel) 2022;12:1974.

28. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(Suppl 2):e1–15.

29. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, *et al.* 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 2019;14:27.

30. Harshit Kumar A, Singh Griwan M. A comparison of APACHE II, BISAP, Ranson's score and modified CTSI in predicting the severity of acute pancreatitis based on the 2012 revised Atlanta Classification. Gastroenterol Rep (Oxf) 2018;6:127–31.

31. Sagar AJ, Khan M, Tapuria N. Evidence-Based Approach to the Surgical Management of Acute Pancreatitis. Surg J (NY) 2022;8:e322–35.

32. Sun H, Zuo HD, Lin Q, Yang DD, Zhou T, Tang MY, *et al.* MR imaging for acute pancreatitis: the current status of clinical applications. Ann Transl Med 2019;7:269.

33. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology 2018;154:1096–101.

34. De Bernardinis M, Violi V, Roncoroni L, Boselli AS, Giunta A, Peracchia A. Discriminant power and information content of Ranson's prognostic signs in acute pancreatitis: a meta-analytic study. Crit Care Med 1999;27:2272–83.

35. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, *et al.* Acute pancreatitis. Lancet 2020;396:726–34.

36. Singh VK, Wu BU, Bollen TL, Repas K, Maurer R, Mortele KJ, *et al.* Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. Clin Gastroenterol Hepatol 2009;7:1247–51.

37. Gupta D, Mandal NS, Arora JK, Soni RK. Comparative Evaluation of Harmless Acute Pancreatitis Score (HAPS) and Bedside Index of Severity in Acute Pancreatitis (BISAP) Scoring System in the Stratification of Prognosis in Acute Pancreatitis. Cureus 2022;14:e32540.

38. Ueda T, Takeyama Y, Yasuda T, Kamei K, Satoi S, Sawa H, *et al.* Utility of the new Japanese severity score and indications for special therapies in acute pancreatitis. J Gastroenterol 2009;44:453–9.

39. Banday IA, Gattoo I, Khan AM, Javeed J, Gupta G, Latief M. Modified Computed Tomography Severity Index for Evaluation of Acute Pancreatitis and its Correlation with Clinical Outcome: A Tertiary Care Hospital Based Observational Study. J Clin Diagn Res 2015;9:TC01–05.

40. Arif A, Jaleel F, Rashid K. Accuracy of BISAP score in prediction of severe acute pancreatitis. Pak J Med Sci 2019;35:1008–12.

41. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut 2008;57:1698–703.

42. Mounzer R, Langmead CJ, Wu BU, Evans AC, Bishehsari F, Muddana V, *et al.* Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. Gastroenterology 2012;142:1476–82.

43. Cho JH, Kim TN, Chung HH, Kim KH. Comparison of scoring systems in predicting the severity of acute pancreatitis. World J Gastroenterol 2015;21:2387–94.

44. Mikó A, Vigh É, Mátrai P, Soós A, Garami A, Balaskó M, *et al.* Computed Tomography Severity Index vs. Other

Indices in the Prediction of Severity and Mortality in Acute Pancreatitis: A Predictive Accuracy Meta-analysis. Front Physiol 2019;10:1002.

45. Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, *et al.* Clinical practice guideline: management of acute pancreatitis. Can J Surg 2016;59:128–40.

46. Farkas N, Hanák L, Mikó A, Bajor J, Sarlós P, Czimmer J, *et al.* A Multicenter, International Cohort Analysis of 1435 Cases to Support Clinical Trial Design in Acute Pancreatitis. Front Physiol 2019;10:1092.

47. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. Am J Gastroenterol 2017;112:1366–72.

48. UK National Institute for Health and Care Excellence. NICE guidelines. Pancreatitis; 2018 [Internet]. Available from: www.nice.org.uk/guidance/ng104 [cited 2025, Apr 11].

49. Singla A, Simons J, Li Y, Csikesz NG, Ng SC, Tseng JF, *et al.* Admission volume determines outcome for patients with acute pancreatitis. Gastroenterology 2009;137:1995–2001.

50. Lankisch PG, Assmus C, Lehnick D, Maisonneuve P, Lowenfels AB. Acute pancreatitis: does gender matter? Dig Dis Sci 2001;46:2470–4.

51. de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, *et al.*; ERICA Consortium. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med 2022;387:989–1000.

52. Di Martino M, Van Laarhoven S, Ielpo B, Ramia JM, Manuel-Vázquez A, Martínez-Pérez A, *et al.* Systematic review and meta-analysis of fluid therapy protocols in acute pancreatitis: type, rate and route. HPB (Oxford) 2021;23:1629–38.

53. Iqbal U, Anwar H, Scribani M. Ringer's lactate versus normal saline in acute pancreatitis: A systematic review and meta-analysis. J Dig Dis 2018;19:335–41.

54. Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. Cochrane Database Syst Rev 2012;2012:CD009779.

55. Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev 2013;2013:CD009179.

56. Jabaudon M, Belhadj-Tahar N, Rimmelé T, Joannes-Boyau O, Bulyez S, Lefrant JY, *et al.*; Azurea Network. Thoracic Epidural Analgesia and Mortality in Acute Pancreatitis: A Multicenter Propensity Analysis. Crit Care Med 2018;46:e198–205.

57. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, *et al.* Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016;17:131–57.

58. Vivian E, Cler L, Conwell D, Coté GA, Dickerman R, Freeman M, *et al.* Acute Pancreatitis Task Force on Quality: Development of Quality Indicators for Acute Pancreatitis Management. Am J Gastroenterol 2019;114:1322–42.

59. Gomes CA, Di Saverio S, Sartelli M, Segallini E, Cilloni N, Pezzilli R, *et al.* Severe acute pancreatitis: eight fundamental steps revised according to the 'PANCREAS' acronym. Ann R Coll Surg Engl 2020;102:555–9.

60. Qi D, Yu B, Huang J, Peng M. Meta-Analysis of Early Enteral Nutrition Provided Within 24 Hours of Admission on Clinical Outcomes in Acute Pancreatitis. JPEN J Parenter Enteral Nutr 2018;42:1139–47.

61. Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev 2010;2010:CD002837.

62. da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, *et al.*; Dutch Pancreatitis Study Group. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet 2015;386:1261–8.

63. Di Martino M, Ielpo B, Pata F, Pellino G, Di Saverio S, Catena F, *et al.*; MANCTRA-1 Collaborative Group. Timing of Cholecystectomy After Moderate and Severe Acute Biliary Pancreatitis. JAMA Surg 2023;158:e233660.

64. Nealon WH, Bawduniak J, Walser EM. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. Ann Surg 2004;239:741–9, discussion 749–51.

65. Hallensleben ND, Timmerhuis HC, Hollemans RA, Pocornie S, van Grinsven J, van Brunschot S, *et al.*; Dutch Pancreatitis Study Group. Optimal timing of cholecystectomy after necrotising biliary pancreatitis. Gut 2022;71:974–82.

66. McDermott J, Kao LS, Keeley JA, Nahmias J, de Virgilio C. Management of Gallstone Pancreatitis: A Review. JAMA Surg 2024;159:818–25.

67. Schepers NJ, Hallensleben ND, Besselink MG, Anten MG, Bollen TL, da Costa DW, *et al.*; Dutch Pancreatitis Study Group. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. Lancet 2020;396:167–76.

68. Tenner S, Vege SS, Sheth SG, Sauer B, Yang A, Conwell DL, *et al.* American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. Am J Gastroenterol 2024;119:419–37.

69. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, *et al.*; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491–502.

70. Diaz JJ Jr, Cullinane DC, Khwaja KA, Tyson GH, Ott M, Jerome R, *et al.* Eastern Association for the Surgery of Trauma: management of the open abdomen, part III-review of abdominal wall reconstruction. J Trauma Acute Care Surg 2013;75:376–86.

71. Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, *et al.*; Dutch Pancreatitis Study Group. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. N Engl J Med 2021;385:1372–81.

72. Trikudanathan G, Tawfik P, Amateau SK, Munigala S, Arain M, Attam R, *et al.* Early (<4 Weeks) Versus Standard (≥ 4 Weeks) Endoscopically Centered Step-Up Interventions for Necrotizing Pancreatitis. Am J Gastroenterol 2018;113:1550–8.

73. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, *et al.*; Dutch Pancreatitis Study Group. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053–61.

74. van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, *et al.*; Dutch Pancreatitis Study Group. Endoscopic or surgical step-up approach

for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51–8.

75. Onnekink AM, Boxhoorn L, Timmerhuis HC, Bac ST, Besselink MG, Boermeester MA, *et al.*; Dutch Pancreatitis Study Group. Endoscopic Versus Surgical Step-Up Approach for Infected Necrotizing Pancreatitis (ExTENSION): Long-term Follow-up of a Randomized Trial. Gastroenterology 2022;163:712–722.e14.

76. Bang JY, Arnoletti JP, Holt BA, Sutton B, Hasan MK, Navaneethan U, *et al.* An Endoscopic Transluminal Approach, Compared With Minimally Invasive Surgery, Reduces Complications and Costs for Patients With Necrotizing Pancreatitis. Gastroenterology 2019;156:1027–1040.e3.

77. Sarathi Patra P, Das K, Bhattacharyya A, Ray S, Hembram J, Sanyal S, *et al.* Natural resolution or intervention for fluid collections in acute severe pancreatitis. Br J Surg 2014;101:1721–8.

78. Arvanitakis M, Dumonceau JM, Albert J, Badaoui A, Bali MA, Barthet M, *et al.* Endoscopic management of acute necrotizing pancreatitis: european Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy 2018;50:524–46.

79. Nealon WH, Walser E. Main pancreatic ductal anatomy can direct choice of modality for treating pancreatic pseudocysts (surgery versus percutaneous drainage). Ann Surg 2002;235:751–8.

80. Bansal A, Gupta P, Singh AK, Shah J, Samanta J, Mandavdhare HS, *et al.* Drainage of pancreatic fluid collections in acute pancreatitis: A comprehensive overview. World J Clin Cases 2022;10:6769–83.

81. Sharma V, Gorsi U, Gupta R, Rana SS. Percutaneous Interventions in Acute Necrotizing Pancreatitis. Trop Gastroenterol 2016;37:4–18.

82. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, *et al.*; Dutch Pancreatitis Study Group. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254–63.

83. Bennett S, Lorenz JM. The role of imaging-guided percutaneous procedures in the multidisciplinary approach to treatment of pancreatic fluid collections. Semin Intervent Radiol 2012;29:314–8.

84. Veitch AM, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, *et al.* Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Endoscopy 2016;48:385–402.

85. Holt BA, Varadarajulu S. The endoscopic management of pancreatic pseudocysts (with videos). Gastrointest Endosc 2015;81:804–12.

86. Panamonta N, Ngamruengphong S, Kijsirichareanchai K, Nugent K, Rakvit A. Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. Eur J Gastroenterol Hepatol 2012;24:1355–62.

87. Muthusamy VR, Chandrasekhara V, Acosta RD, Bruining DH, Chathadi KV, Eloubeidi MA, *et al.*; ASGE Standards of Practice Committee. The role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms. Gastrointest Endosc 2016;84:1–9.

88. Yang D, Amin S, Gonzalez S, Mullady D, Hasak S, Gaddam S, *et al.* Transpapillary drainage has no added benefit on treatment outcomes in patients undergoing EUS-guided transmural drainage of pancreatic pseudocysts: a large multicenter study. Gastrointest Endosc 2016;83:720–9.

89. Binmoeller KF, Nett A. The Evolution of Endoscopic Cystgastrostomy. Gastrointest Endosc Clin N Am 2018;28:143–56.

90. Rodrigues-Pinto E, Baron TH. Evaluation of the AXIOS stent for the treatment of pancreatic fluid collections. Expert Rev Med Devices 2016;13:793–805.

91. Rana SS, Bhasin DK, Sharma RK, Kathiresan J, Gupta R. Do the morphological features of walled off pancreatic necrosis on endoscopic ultrasound determine the outcome of endoscopic transmural drainage? Endosc Ultrasound 2014;3:118–22.

92. Gornals JB, Consiglieri CF, Busquets J, Salord S, dela-Hera M, Secanella L, *et al.* Endoscopic necrosectomy of walled-off pancreatic necrosis using a lumen-apposing metal stent and irrigation technique. Surg Endosc 2016;30:2592–602.

93. Bang JY, Wilcox CM, Navaneethan U, Hasan MK, Peter S, Christein J, *et al.* Impact of Disconnected Pancreatic Duct Syndrome on the Endoscopic Management of Pancreatic Fluid Collections. Ann Surg 2018;267:561–8.

94. Jang JW, Kim MH, Oh D, Cho DH, Song TJ, Park DH, *et al.* Factors and outcomes associated with pancreatic duct disruption in patients with acute necrotizing pancreatitis. Pancreatology 2016;16:958–65.

95. Zerem E, Imširović B, Loga-Zec S, Kunosić S, Hujdurović A, Zerem O. Treatment of Recurrent Pancreatic Pseudocysts with Proven Communication between Pseudocyst and Pancreatic Duct by Long-term Percutaneous Drainage. Ann Acad Med Singap 2015;44:542–4.

96. Nadkarni NA, Kotwal V, Sarr MG, Swaroop Vege S. Disconnected Pancreatic Duct Syndrome: Endoscopic Stent or Surgeon's Knife? Pancreas 2015;44:16–22.

97. Gao L, Zhang JZ, Gao K, Zhou J, Li G, Li BQ, *et al.* Management of colonic fistulas in patients with infected pancreatic necrosis being treated with a step-up approach. HPB (Oxford) 2020;22:1738–44.

98. Evans RP, Mourad MM, Pall G, Fisher SG, Bramhall SR. Pancreatitis: preventing catastrophic haemorrhage. World J Gastroenterol 2017;23:5460–8.

99. Balachandra S, Siriwardena AK. Systematic appraisal of the management of the major vascular complications of pancreatitis. Am J Surg 2005;190:489–95.

100. Harris S, Nadkarni NA, Naina HV, Vege SS. Splanchnic vein thrombosis in acute pancreatitis: a single-center experience. Pancreas 2013;42:1251–4.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Guido Basile contributed to conception and design of the paper. All authors have participated to drafting the manuscript and contributed to the literature search. Guido Basile, Marco Vacante and Giuseppe Evola revised the manuscript. All authors have read and approved the final version of the manuscript.

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