European Journal of Internal Medicine 133 (2025) 1–13

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Practical management of severe acute pancreatitis

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ARTICLE INFO

Keywords:
Pancreas
Gastroenterology
Emergency medicine
Critical illness
Acute necrotizing pancreatitis
Endoscopy
Self expandable metallic stents

ABSTRACT

Acute pancreatitis (AP) represents one of the most common reasons for hospital admission and intensive care treatment in internal medicine. The incidence of AP is increasing, posing significant financial burden on healthcare systems due to the necessity for frequent medical interventions. Severe acute pancreatitis (SAP) is a potentially life-threatening condition with substantial morbidity and mortality. The management of SAP requires prolonged hospitalization and the expertise of a multidisciplinary team, comprising emergency physicians, intensivists, internists, gastroenterologists, visceral surgeons, and experts in nutrition, infectious disease, endoscopy, as well as diagnostic and interventional radiology. Effective management and beneficial patient outcomes depend on continuous interdisciplinary collaboration.

This review synthesizes recent evidence guiding the practical management of SAP, with a particular focus on emergency and intensive care settings. Both established as well as new diagnostic and therapeutic paradigms are highlighted, including workup, risk stratification, fluid management, analgesia, nutrition, organ support, imaging modalities and their timing, along with anti-infective strategies. Furthermore, the review explores interventions for local and vascular complications of SAP, with particular attention to the indications, timing and selection between endoscopic (both endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS)), percutaneous and surgical approaches. Similarly, the management of biliary AP due to obstructive gallstones, including the imaging, timing of ERCP and cholecystectomy, are discussed. By integrating new evidence with relevant guidance for everyday clinical practice, this review aims to enhance the interdisciplinary approach essential for improving outcomes in SAP management.

1. Initial management

1.1. Diagnosis

Diagnosis of acute pancreatitis (AP) is based on the Revised Atlanta Classification[1] (Table 1) requiring at least two of three criteria: i) typical epigastric pain radiating to the back, ii) serum lipase (or the less specific amylase) levels elevated at least three times their upper limit of normal and/or iii) characteristic imaging findings. Other causes of elevated lipase should be considered in unclear cases (Table 2) [2–4]. Imaging in the emergency room (ER) is only necessary to confirm AP in atypical presentation, in case of doubt or when other life-threatening conditions must be excluded. For this, an abdominal ultrasound may suffice. CT for assessment of severity or complications should be

Abbreviations: ABP, Acute biliary pancreatitis; ACS, Abdominal compartment syndrome; AIT, Anti-infective therapy; ANC, Acute necrotic collection; ANP, Acute necrotizing pancreatitis; AP, Acute pancreatitis; APFC, Acute peripancreatic fluid collection; BUN, Blood urea nitrogen; CBD, Common bile duct; CCY, Cholecystectomy; CRP, C-reactive protein; CT, Computed tomography; DPDS, Disconnected pancreatic duct syndrome; EN, Enteral nutrition; ER, Emergency room; ERCP, Endoscopic retrograde cholangiopancreatography; ESPEN, European Society for Clinical Nutrition and Metabolism; EUS, Endoscopic ultrasound; IAP, Intraabdominal pressure; ICU, Intensive care unit; LAMS, Lumen-apposing metal stent; MAP, Mean arterial pressure; MPD, Main pancreatic duct; MRCP, Magnetic resonance cholangiopancreatography; MRI, Magnetic resonance imaging; PEEP, positive end-expiratory pressure; PFC, Peripancreatic fluid collection; PP, Pancreatic pseudocyst; PCT, Procalcitonin; PS, Plastic stents; RCT, Randomized controlled trial;SAP, Severe acute pancreatitis; SIRS, Systemic inflammatory response syndrome; TPN, Total parenteral nutrition; VARD, Video-assisted retroperitoneal drainage; WON, Walled-off necrosis.

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https://doi.org/10.1016/j.ejim.2024.10.030
Received 31 July 2024; Received in revised form 29 October 2024; Accepted 30 October 2024
Available online 29 November 2024

Table 1
Severity grades of acute pancreatitis based on the revised Atlanta classification.

Pancreatitis Severity Grade (Revised Atlanta Classification)
Mild acute pancreatitis (MAP): • No organ failure • No local or systemic complications **Moderately severe acute pancreatitis (MSAP):** • Organ failure that resolves within 48 h (transient organ failure) *AND/OR* • Local or systemic complications without persistent organ failure **Severe acute pancreatitis (SAP):** • Persistent organ failure (>48 h) of one or several organs

The revised Atlanta classification from 2012 is an international consensus for classifying the severity of acute pancreatitis. It also provides standardized terminology for its complications (not shown here).

Table 2
Possible conditions associated with elevated serum amylase or lipase.

Conditions associated with elevated amylase	Conditions associated with elevated lipase
• Macroamylasemia • Pancreatic disease (e.g., pancreatitis, complications of pancreatitis, trauma, surgery, ERCP, ductal obstruction, tumor, cystic fibrosis) • Gastrointestinal disease (e.g., cholecystitis, appendicitis, obstruction, perforation, complicated peptic ulcer, celiac disease, IBD, severe gastroenteritis, acute mesenteric ischemia, abdominal aortic aneurysm) • Gynecologic disease (e.g., pregnancy, ectopic pregnancy, ovarian cysts, pelvic inflammatory disease) • Renal failure • Liver failure or cirrhosis • Pulmonary diseases (e.g., ARDS, pneumonia, embolism, infarction, neoplasm) • Type 2 diabetes or ketoacidosis • Surgery or trauma (abdominal, cardiac) • Shock • Skin injuries (e.g., severe burns, Toxic Epidermal Necrolysis, Steven Johnson Syndrome) • Infectious diseases (e.g., HIV, COVID-19) • Transplant (liver, kidney, heart or bone marrow) • Neoplasms • Drugs • Salivary gland disease • Anorexa nervosa, bulimia • Alcoholism • Idiopathic	• Macrolipasemia • Pancreatic disease (e.g., pancreatitis, complications of pancreatitis, trauma, surgery, ERCP, ductal obstruction, tumor) • Gastrointestinal disease (e.g., cholecystitis, appendicitis, obstruction, perforation, complicated peptic ulcer, celiac disease, IBD, severe gastroenteritis, acute mesenteric ischemia, abdominal aortic aneurysm) • Renal failure • Liver failure • Pulmonary diseases (e.g., ARDS, pneumonia, embolism, infarction, neoplasm) • Type 2 diabetes or ketoacidosis • Surgery or trauma (abdominal, cardiac) • Shock • Skin injuries (e.g., severe burns, Toxic Epidermal Necrolysis, Steven Johnson Syndrome) • Infectious diseases (e.g.: HIV, COVID-19) • Transplant (liver, kidney, heart or bone marrow) • Hypertriglyceridemia • Drugs • Alcoholism • Idiopathic

There are multiple causes for elevated amylase and/or lipase in the serum. It is sufficient to measure on of these enzymes while serum lipase is more specific than serum amylase for diagnosing acute pancreatitis.
Abbreviations: ARDS: acute respiratory distress syndrome, COVID-19: coronavirus infection disease 19; HCV: hepatitis C virus; HIV: human immunodeficiency virus; ERCP: endoscopic retrograde cholangiopancreatography; IBD: inflammatory bowel disease.

postponed for at least 48–96 h as performing it earlier might underestimate them [1,3,5].

Initial laboratory workup includes blood cell count, electrolytes, creatinine, blood urea nitrogen (BUN), cholestasis parameters, and C-reactive protein. Further details are provided in Fig. 1.

1.2. Treatment

Although no specific therapy for the early phase is available, fluid resuscitation (FR), adequate pain management, as well as nutritional support are key steps that should be initiated as early as possible.

Regarding FR, several trials have compared lactated Ringer's versus normal saline. Recent guidelines[3] suggest lactated Ringer's as the preferred fluid based on meta-analyses that show some benefits (e.g., less systemic inflammation, admission to the intensive care unit (ICU) and local complications) [6,7]. However, data are heterogeneous warranting additional research. Likely more important than the fluid type is the fluid rate. In a recent randomized controlled trial (RCT)[8], moderate FR was less likely to cause fluid overload than aggressive FR with similar clinical outcomes. Accordingly, in patients without hypovolemia, a fluid rate of 1.5 ml/kg/hour appeared to be the preferred choice. In case of hypovolemia, a bolus of 10 ml/kg in two hours should be administered first. An important aspect was the regular assessment of the volume status consecutively adjusting the fluid rate. Intravenous fluids can be discontinued once the patient tolerates oral feeding and seems euvolemic[9]. In patients with difficulties in volume management or with hemodynamic impairment, special care should be taken to avoid fluid overload (details in Fig. 1).

Effective pain management is essential and should also be initiated as soon as possible. However, as evidence is scarce, no clear strategy for pain control can be recommended. Opioids and non-steroidal anti-inflammatory drugs are frequently used and meta-analyses have shown no difference in pain control in the first hours of admission or the need for rescue analgesia[10]. Metamizol, where available, is a good alternative although more studies are needed for confirmation[11]. A recent RCT has also evaluated the role of cyclooxygenase-2 inhibitors with better pain relief and less severe AP but confirmation is also needed[12]. Epidural analgesia had been suggested as a good option for pain control and was associated with reduced mortality[13], but a recent RCT failed to prove these results[14].

Regarding nutrition, several RCTs have shown that early oral feeding is safe and associated with a shorter hospital stay and costs without increasing complications. Hence, if patients tolerate food, they should start a low-fat solid diet as soon as possible [15–18]. If oral feeding is not tolerated/feasible, enteral nutrition (EN) can be considered (details in the ICU chapter).

1.3. Etiology workup

A first approach to etiology should be part of initial management as some AP causes need specific treatment which in turn avoid AP

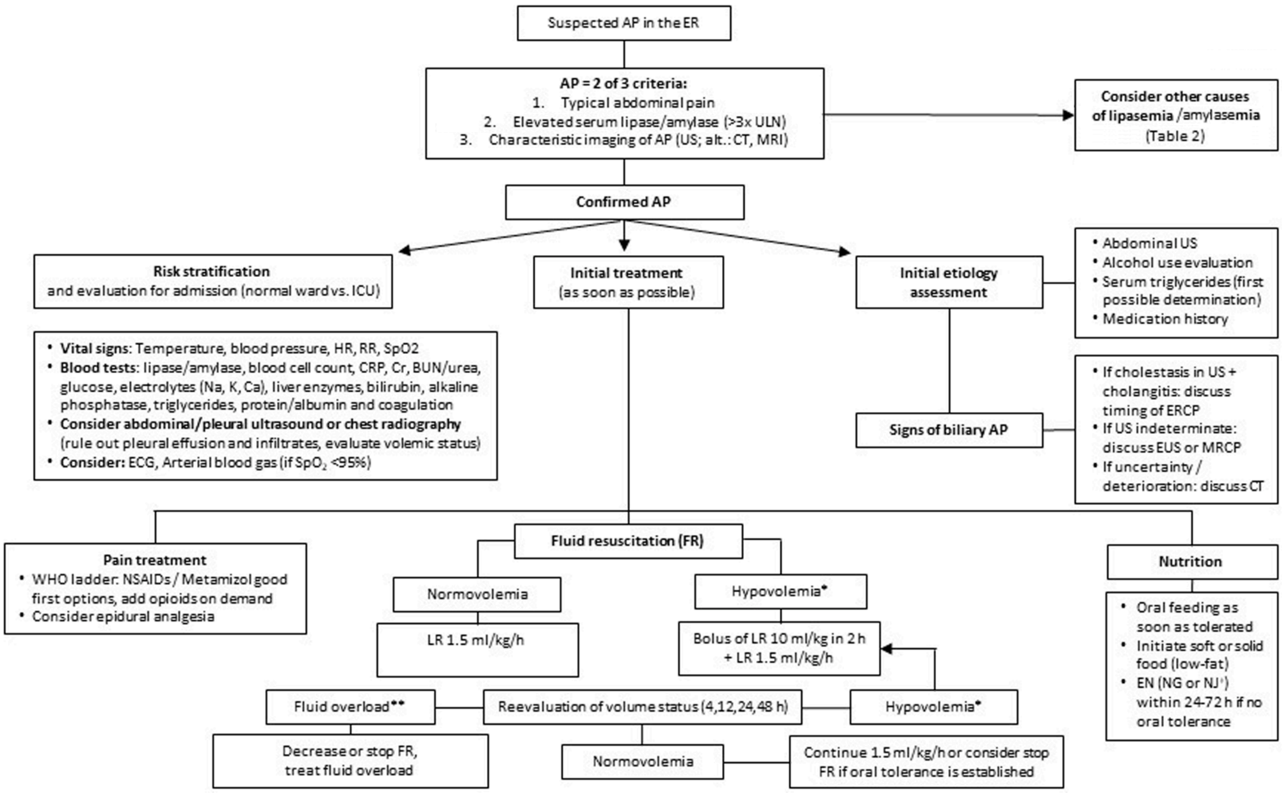

Fig. 1. Initial management of acute pancreatitis (AP) in the emergency room (ER).
A proposed algorithm of the most important diagnostic and therapeutic measures that should be performed in the ER are depicted. * Hypovolemia criteria[8]: Baseline creatinine >1.1 mg/dL or blood urea nitrogen (BUN) >20 mg/dL (equivalent to urea >42.8 mg/dL), hematocrit >44%, increase in creatinine and/or BUN and/or urea from the previous value, urine output <0.75 mL/kg/h, systolic blood pressure <90 mmHg without other explanation than hypovolemia, signs and/or symptoms of dehydration. ** Fluid overload [8]: Suspicion of fluid overload defined by the presence of at least 1 of the following 3 criteria, definitive fluid overload at least 2: i) Hemodynamic-imaging evidence (at least 1): A. Non-invasive diagnostic evidence of heart failure (i.e., echocardiographic) B. Radiographic evidence of pulmonary congestion C. Invasive hemodynamic monitoring suggesting evidence of heart failure [i.e.,pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) >18mmHg, right arterial pressure (or central venous pressure) >12 mmHg, or cardiac index <2.2 L/min per m2], ii) symptoms: dyspnea and iii) signs (at least 1): A. Peripheral edema B. Pulmonary rales C. Increased jugular venous pressure or hepatojugular reflux, or both. + *a* NJ tube may be considered in case of gastric outlet obstruction. Abbreviations: alt.: alternatively; CRP: C-reactive protein; Ca, calcium; Cr: creatinine; CT: computed tomography; EN: enteral nutrition; ECG: electrocardiogram; ER: emergency room; EUS: endoscopic ultrasound; FR: fluid resuscitation; h: hour; HR: heart rate; ICU: Intensive care unit; K, potassium; Kg: kilogram; LR: lactated Ringer solution; ml: milliliter; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; Na, sodium; NG: nasogastric tube; NJ: nasojejunal tube; NSAIDs: non-steroidal anti-inflammatory drugs; RR: respiratory rate; SpO2: peripheral oxygen saturation; ULN: upper limit of normal reference value; US: ultrasound; WHO: World Health Organization.

Table 3
Possible etiologies of acute pancreatitis.

Causes of acute pancreatitis
Gallstones
Alcohol
Hypertriglyceridemia (usually >1000 mg/dl)
Drugs (e.g. thiopurines, asparaginase, didanosine, valproic acid, mesalamine)
Post-ERCP
Post- trauma (blunt or penetrating force) or postoperative
Autoimmune pancreatitis (Type 1 and 2)
Infectious diseases (e.g. cytomegalovirus, Mumps virus, Epstein-Barr virus, toxoplasma)
Hypercalcemia (e.g. Primary hyperparathyroidism)
Anatomical anomalies (pancreas divisum, annular pancreas)
Obstructive (pancreatic tumors or cysts, more frequently IPMN)
Toxins (e.g., scorpion bites)
Sphincter of Oddi Dysfunction
Genetic alterations (PRSS1, CFTR, SPINK1, CTRC)
Associated conditions: diabetes, obesity, smoking

The most common/typical reasons for acute pancreatitis are listed above from more to less frequent. However, despite the various etiologies that are not fully listed here, some cases remain idiopathic.
Abbreviations: AP: acute pancreatitis; CFTR: cystic fibrosis transmembrane conductance regulator; CTRC: chymotrypsin C channel; ERCP: endoscopic retrograde cholangiopancreatography; PRSS1: serine protease 1; IPMN: intraductal papillary mucinous neoplasm; SPINK1: serine protease inhibitor Kazal type 1.

recurrence. Gallstones are the major cause of AP; hence, abdominal ultrasound (within 48 h) should be performed [15,19–21]. Elevated liver enzymes orientate this diagnosis with high positive predictive value. In case of normal ultrasound, but elevated liver enzymes, a second ultrasound should be considered as the accuracy increases around 20% [22, 23]. If biliary etiology is still suspected, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS, with better diagnostic yield although less available) should be performed. [24,25] However, it seems that the diagnostic yield of EUS is better after recovery.[26] Alcohol as the second most common cause should be evaluated to determine the need for withdrawal treatment [15,27–29]. Hypertriglyceridemia is another treatable cause with specific management, hence serum triglyceride levels should be obtained early [15,19, 28]. Medication history should be reviewed to avoid potentially etiologic drugs [15,19,28]. Further causes are given in Table 3.

2. Risk stratification

About 20–40% develop severe acute pancreatitis (SAP), which can be associated with single or multiple organ dysfunction requiring intensive care [30,31]. As SAP is associated with mortality rates up to 30%, prompt identification of patients who are prone for organ failure at an

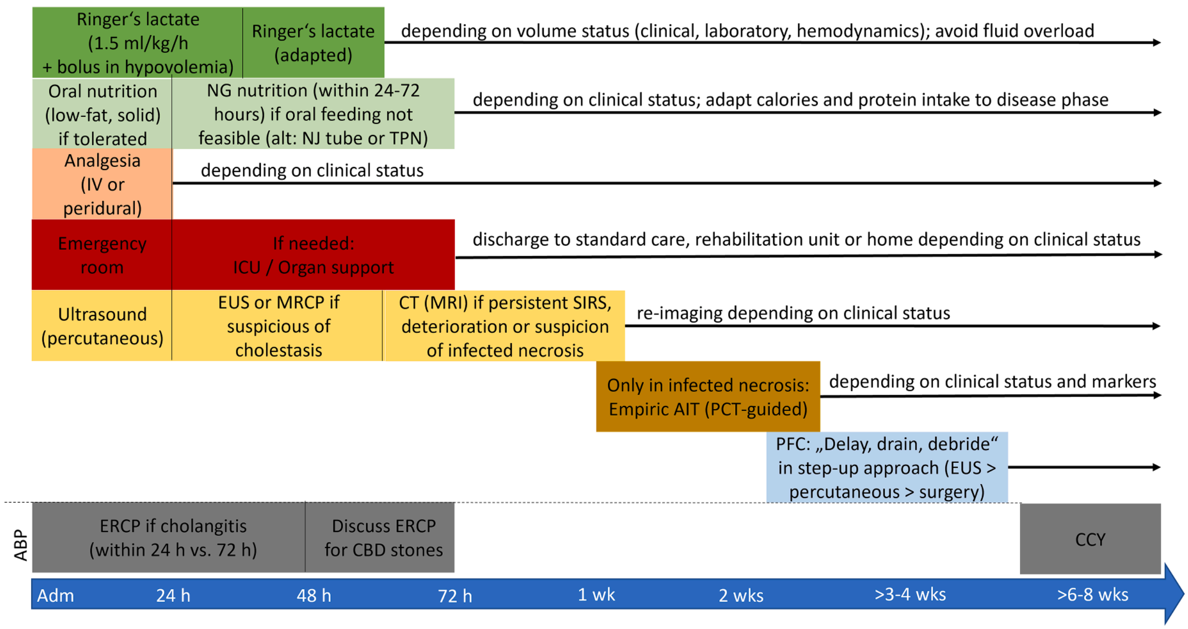

Fig. 2. Timing of management measures in severe acute pancreatitis.
The typical timeline of the most relevant management measures in severe acute pancreatitis is depicted. The lowest row applies to acute biliary pancreatitis (ABP) while all other management measures apply to all etiologies. In ABP, the indications for ERCP are mainly restricted to cholangitis and persistent choledocholithiasis (with a tendency to longer time intervals). In the follow-up phase after discharge, patients should be evaluated for signs of chronic pancreatitis (e.g., diabetes mellitus, exocrine pancreatic insufficiency) and obstructive symptoms that may arise from PFC. In patients >40 years old and idiopathic AP, cross-sectional imaging to rule out pancreatic cancer should be performed at the latest 3 months after AP onset. In case of PFC drainage, a magnetic resonance cholangiopancreatography (or contrast-enhanced computed tomography) should be evaluated to ascertain the presence of disconnected pancreatic duct syndrome and to quantify the resolution of PFC in order to determine further drainage therapy. Abbreviations: Adm, admission; ABP, acute biliary pancreatitis; AIT, anti-infective therapy; CBD, common bile duct; CCY, cholecystectomy; CT, computed tomography (contrast-enhanced); EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; h, hour; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging (contrast-enhanced); NG, nasogastric; NJ, nasojejunal; PCT, procalcitonin; PFC, peripancreatic fluid collection; SIRS, systemic inflammatory response syndrome; TPN, total parenteral nutrition; wk/wks, week/weeks.

early stage is important [29,30].

Parameters that are typically associated with SAP are summarized in table 5[3]. Scoring systems for risk stratification and prediction of SAP were widely developed, however, evidence on their predictive performance is variable[30]. Hence, scores should not supersede clinical assessment. Their value rather lies in excluding a severe course (good negative predictive value) while there is no score that is universally effective across all forms of AP [29,31,32]. Within the scoring landscape, the Ranson criteria, the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Simplified Acute Physiology Score (SAPS II), Sequential Organ Failure Assessment (SOFA), CT severity index (CTSI), and the Bedside Index of Severity in Acute Pancreatitis (BISAP) score are the most recommended [32,33]. As all these scores have their place in SAP management, the BISAP score is regarded as probably the most accurate and applicable in routine practice for predicting severity, death, and organ failure [32,33].

As there are no SAP-specific criteria for ICU admission, proper clinical judgement, ideally in a multidisciplinary approach, will be necessary to decide whether a patient should be admitted to the normal ward, intermediate care or intensive care unit.

3. Intensive care therapy

The management of SAP in the ICU is primarily supportive and based on fluid administration, enteral nutrition, organ support, and, anti-infective treatment; all of which adapted to the disease phase (Fig. 2). Patients and their relatives should be informed early on that the hospital stay might be rather long and that social workers and psychologists can support.

3.1. Fluid management

SAP is characterized by a systemic inflammatory response syndrome with capillary leakage, intravascular loss of fluid, and vasodilatation [34,35]. This results in hypovolemic and distributive shock, which in turn causes severe microcirculatory dysfunction and ultimately multi-organ failure[36]. In general, early FR is regarded as the initial fundamental treatment [29,37–39]. However, an individually tailored volume management is essential to avoid the deleterious effects of fluid overload (e.g., acute respiratory distress syndrome or abdominal compartment syndrome (ACS))[40].

ACS is defined as an intra-abdominal pressure (IAP) >20 mmHg (measured via urinary bladder catheter) with concomitant new onset of organ dysfunction. ACS, due to its high morbidity and mortality, requires urgent management (Table 5). However, interventional management of ACS is controversial (e.g., timing, modality) as adequately designed RCTs are lacking [41,42]. However, decompressive laparotomy is effective in rapidly reducing IAP[42]. Hence, multidisciplinary team discussion should weigh the morbidity and complications of an open abdomen after decompressive laparotomy against the risks of inadequately treated ACS.

Hemoconcentration and increased blood viscosity may serve as drivers of pancreatic necrosis, resulting from pancreatic hypoperfusion [43]. Clinical targets for volume therapy in SAP include noninvasive clinical markers (e.g. mean arterial pressure [MAP], heart rate, urine output, skin mottling score, capillary refill time), invasive hemodynamic parameters (e.g. transpulmonary thermodilution) and laboratory values (e.g. lactate, hematocrit, BUN) [44–46] (Table 5). An elevated hematocrit at admission and failure to achieve a reduction of hematocrit within the first 24 h is associated with an adverse prognosis[46] (Table 4). BUN levels ≥20 mg/dL at admission have been linked to

Table 4
Risk factors of adverse prognosis in acute pancreatitis.

Parameters associated with increased risk of a severe disease course	
SIRS (≥2 criteria)	- Temperature <36 °C or >38 °C - HR >90/min - RR >20/min (or PaCO2 <32 mmHg) - White blood count >12 G/L or <4 G/L (or >10% immature leukocytes)
Laboratory values	- Hematocrit ≥40% (women) / ≥44% (men) (or rising hematocrit) - Calcium <1,97 mmol/l on admission or within 48 h - Glucose >200 mg/dL - CRP >15 mg/dL within 48–72 h - BUN ≥20 mg/dL / Urea ≥42.8 mg/dL (or rising BUN) - Creatinine >ULN - LDH >350 U/L
Scoring systems	- BISAP ≥3 points - SOFA elevation ≥2 points - APACHE-II ≥8 points on admission or within first 72 h
Patient characteristics	- Age >55–60 years - BMI ≥25–30 kg/m² - Alcohol misuse - Altered mental status - Comorbid disease
Radiology findings	- Pleural effusions - Pulmonary infiltrates - Multiple or extensive peripancreatic fluid collections

Some of the most relevant parameters that are associated with an unfavorable disease course for initial risk assessment are listed. Within the scoring landscape, the Ranson criteria, the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Simplified Acute Physiology Score (SAPS II), Sequential Organ Failure Assessment (SOFA), CT severity index (CTSI), and the Bedside Index of Severity in Acute Pancreatitis (BISAP) score are the most recommended. However, while the scores are helpful in excluding a severe disease course, they are of limited value in predicting a severe course (relatively good negative predictive value, moderate positive predictive value).
Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; HR, heart rate; LDH, lactate dehydrogenase; RR, respiratory rate; SIRS, systemic inflammatory response syndrome; ULN, upper limit of normal.

progressive organ failure and mortality[47]. However, the specificity is low because an increase in BUN can be multifactorial (e.g., renal failure, increased protein catabolism or gastrointestinal bleeding).

After the first 24–48 h, the FR should be adapted as outlined earlier (Fig. 1). This reduction should be conducted under the guidance of close clinical and hemodynamic monitoring, with the objective of achieving defined rehydration goals[48]. These commonly comprise the extent of urinary output and clinical signs of hemodynamic stabilization such as reversal of tachycardia and hypotension as well as improvement of serum lactate. There are no reliable data on the correct amount and rate of fluid requirement for SAP after initial FR[49]. Moreover, no high-quality evidence on how to use invasive hemodynamic monitoring for guiding fluid management is available. However, the use of less invasive techniques to evaluate the fluid status in SAP (e.g., ultrasound) should further be evaluated [50,51].

3.2. Nutritional support

The historic concept of “pancreatic rest” (initiation of oral feeding only after resolution of abdominal pain and normalization of pancreatic enzymes), has been replaced by the concept of “early nutrition”. Nutrition within 24–72 h after admission reduces the incidence of bacterial translocation, thus, reducing systemic inflammation and maintaining gut integrity and gut microbiota composition[52]. Metanalyses, comparing early and delayed (after 48 h) EN demonstrated benefits of early EN with regard to incidence of infections, organ failure and length of ICU stay [53,54]. However, there is insufficient evidence of a clear clinical benefit of early EN via a tube (as compared to the benefits of early oral feeding) [54,55]. The ESPEN guideline recommends initiation of EN within 24–72 h of admission.

In non-ventilated, conscious patients, without nausea and vomiting, and no signs of severe ileus or gastrointestinal luminal obstruction an immediate trial of oral nutrition should be performed (Table 5)[56]. When oral nutrition is not tolerated or feasible, EN can be performed either via nasogastric, nasoduodenal or nasojejunal tubes. All of these tubes are safe and well-tolerated, however, the usual route should be nasogastric [57–59]. Nasojejunual tubes are particularly indicated in clinical situations of delayed gastric emptying or large-volume reflux (e.g., gastric outlet obstruction). Standard polymer feeding formulations should be used routinely. The higher costs associated with more expensive (semi)-elemental formulations do not appear to be justified by any proven benefits in terms of feeding tolerance and infections.

An initial energy requirement of 15–20 kcal/kg/d and protein requirement of 1.2–1.5 g/kg/d is recommended[58]. Total parental nutrition (TPN) should be considered only in clinical situations where oral or enteral feeding is not feasible or sufficient [55,60]. In patients with SAP and IAP of 15–20 mmHg, EN should be performed via nasojejunal tubes, with a starting volume of 20 ml/h under continuous abdominal monitoring. In the presence of ACS, EN should be discontinued and TPN initiated[58].

3.3. Anti-infective strategies

The clinical course of SAP can deteriorate dramatically due to the occurrence of hospital-acquired infections, such as cholangitis, pneumonia, line-sepsis, bacteremia or later infection of pancreatic necrosis [20].

Approximately 10–20% of all patients with AP will develop necrosis involving both the pancreas and peripancreatic tissues. In approximately one-third of cases, the necrotic tissue becomes infected with bacteria or fungi[61]. The mortality rate associated with infected pancreatic necrosis is up to 20–30%, which is twice as high as in cases of sterile pancreatic necrosis[62]. Infection of necroses typically occur during weeks 2 to 4 of illness and are generally not the cause of deterioration in the early disease course[63]. Bacterial infections are monomicrobial in 60–87% of patients while polymicrobial in 10–40% and mostly caused by gram-negative anaerobes[64].

An infected necrosis is to be suspected if gas inclusions are seen in the area of pancreatic or peripancreatic collection in cross-sectional imaging, if the patient’s clinical condition deteriorates (e.g. fever, bacteremia, leukocytosis, procalcitonin increase, organ dysfunction) or in case of positive blood cultures[56]. CT- or EUS-guided fine-needle aspiration for gram stain and cultures is usually unnecessary and may cause secondary infection due to aspiration[3].

When infected necrosis is suspected, initiation of broad-spectrum intravenous antibiotics with sufficient penetration into pancreatic necrosis is recommended (Table 5). Antibiotics that meet this criterion are carbapenems, quinolones, metronidazole, and third- or higher-generation cephalosporins. Antifungal therapy should only be used for definitive fungal infections, which typically occur in patients with prolonged ICU stay, under antibiotic treatment, in case of indwelling catheters and TPN[56].

Current guidelines, with the exception of Japanese guidelines, do not recommend routine use of prophylactic antibiotic therapy in cases of predicted SAP or sterile necrosis [29,37–39,65–67]. Prophylactic antibiotic therapy does not reduce infection of necrosis but increases the risk of antibiotic multidrug resistance and fungal superinfection which ultimately worsens the prognosis[68]. It is noteworthy that adherence to these recommendations remains low. In a Dutch study[69], the majority of patients received antibiotics, typically administered too early in the disease course without a proven infection. Moreover, empirical antibiotics were inappropriate based on pancreatic cultures in half the cases.

The data on selective bowel decontamination in SAP is rather scarce. While older studies suggested some benefits, some studies hint towards an increased risk of fungal infects and, overall, the benefits of bowel

Table 5
Intensive care treatment of severe acute pancreatitis (SAP).

ICU management	Do's	Don'ts	Target values
Fluid management	- Vasopressors if hypotensive in euvolemia - Neutral fluid balance if stable - Negative balance if signs of fluid overload - Fluid bolus of 5ml/kg/KG over 30 min if refractory hypotension - Prefer balanced solutions (e.g. Ringer's lactate)	- Fluid overload - Severe hypovolemia - Shock - Vasopressors without prior fluid resuscitation - Colloids (e.g., HAES)	- *Clinical* - HR <120/min, MAP 65-85 mmHg, UO >0,5 ml/kg/h, improvement of SMS, CRT<3 sec. - *Invasive hemodynamics* - Transpulmonary thermodilution (e.g. CCO normalization, ITBI 850-1000 mL/m^2) - *Laboratory* - Lactate <2mmol/L, hematocrit↓, BUN↓
Abdominal Compartment Syndrome (ACS)	- Measure IAP (indirectly via urinary bladder catheter) every 4 hours - Volume-reducing measures (e.g., diuretics, RRT, drainage of ascites or pleural effusion) - Treatment of paralytic ileus (e.g., laxatives, prokinetics, decompression catheter) - Adapt ventilation (PEEP, consider neuromuscular blockade) - Multidiscplinary discussion of decompressive laparotomy (early)	- Irregular MAP measurements - Fluid overload - Decompressive laparotomy without a trial of conservative management - EN in established ACS	- Adjust MAP to IAP → Target: APP >60 mmHg (APP = MAP – IAP) - Adjust PEEP to IAP
Nutritional support	- Early oral feeding if tolerated/feasible - If EN: NG tubes; in case of gastric outlet obstruction or reflux: NJ tubes - Standard formulations - EN in IAP↑ and open abdominal wall under abdominal surveillance - Adapt calories and protein to disease phase, BMI, high-volume external drains and dialysis	- Pancreatic rest - Malnutrition - Overfeeding in the initial phase - EN if oral feeding is feasible - TPN if EN is feasible - EN when general contraindications for EN exist (e.g., hemodynamic instability, intestinal obstruction or leakage)	- Initiation of EN within 24-72h after admission - Calories: initially 15-20 kcal/kg/d - Protein: initially 1.2-1.5 g/kg/d
Anti-infective strategies	- Suspect infection clinically and in imaging - Empiric broad-spectrum AIT with sufficient pancreatic penetration (e.g., carbapenems, third- or higher-generation cephalosporins) - PCT to guide initiation, continuation, discontinuation of AIT	- CT-or EUS-guided fine-needle aspiration - Prophylactic AIT - Empiric anti-fungal therapy - Selective bowel decontamination - Enteral probiotics	- Infected pancreatic necrosis: mostly monomicrobial, gram-negative anaerobes - Threshold PCT of 1.0 ng/mL to guide AIT
Imaging	- Abdominal ultrasound for the assessment of volemic status or complications (ascites, pleural effusions) - CT if suspicious of infected necrosis or complication - Consider chest radiograph for assessment of pleural effusions and infiltrates (typically left-sided) - Consider bedside EUS in patients difficult to transport to CT/MRI	- Early CT (<48h of presentation) for assessment of severity or complications	- Use serial abdominal ultrasounds for monitoring - Postpone CT if there are no diagnostic doubts

decontamination in several other critical illnesses is quite controversial [70–72]. In terms of antibiotic stewardship a general bowel decontamination or all SAP patients appears unjustified.

To avoid indiscriminate use of antiinfectives, procalcitonin testing has been demonstrated as a helpful tool. In a RCT, procalcitonin was used at admission, day 4 and day 7, and then weekly with a threshold of 1.0 ng/ml to guide the initiation, continuation and discontinuation of antibiotic therapy[73]. This approach reduced the likelihood of initiation and duration of antibiotic use without increasing infection rates.

4. Management of acute biliary pancreatitis (ABP)

4.1. Diagnosis and treatment of ABP

While most gallstones pass spontaneously into the duodenum, imaging is required to ascertain the presence of intra- or extrahepatic cholestasis. Non-invasive imaging (primarily ultrasound; alternatively CT or MRI) is typically preferred to determine further management. EUS can be also used primarily due to its high sensitivity. In unclear cases, MRCP or EUS clarify whether a stone obstructs the ampulla of Vater or common bile duct (CBD) while EUS showed superior accuracy for diagnosing CBD stones or sludge[24]. In critically ill patients, invasive EUS may be favored as transportation is not required and as, in case of an intubated patient, no MRI-compatible equipment is necessary.

Controversies exist regarding the indication (cholestasis alone vs. cholangitis) and timing (urgent vs. elective) of endoscopic retrograde cholangiopancreatography (ERCP). While previous studies suggested ERCP within 24 h in patients with choledocholithiasis [74,75], recent evidence show that ERCP is only indicated in the presence of cholangitis or persistent choledocholithiasis[76] and that a time window of 72 h may suffice [77,78]. Hence, the routine use of urgent ERCP is discouraged in multiple guidelines[15]. Nevertheless, some national guidelines still recommend an ERCP within 24 h after admission in the case of cholangitis and within 72 h after symptom onset in choledocholithiasis [3,79]. Interestingly, there is no compelling evidence supporting that sphincterotomy reduces the risk of recurrent biliary events[80]. Moreover, the use of biliary plastic stents (PS) before cholecystectomy (CCY) remains unclear. Although a recent RCT showed no superiority in the PS group regarding recurrence of biliary events, patients with SAP were not included[81].

Taken together, in severe ABP, an increasing body of evidence indicates a more personalized approach regarding detection and clearance of impacted gallstones (Fig. 2).

4.2. Cholecystectomy in ABP

While CCY is clearly indicated, there is an ongoing debate regarding its timing[30]. On the one hand, postponing CCY may result in recurrent ABP, cholecystitis or cholangitis, even in patients with sphincterotomy. On the other hand, there is fear of peri- and postoperative complications [80,82]. In mild ABP, early CCY within 24 h after admission or at least during the same admission appeared beneficial [83–85]. Of note, severity grading is only established at 48 h after symptom onset – a timepoint at which CCY in mild ABP should already have been performed. In moderate ABP, early CCY within 48 h was superior in one RCT[86] while a large cohort study of moderate and severe ABP revealed increased risk of morbidity and mortality after early CCY[87]. Predictors of mortality were presence of complication of ABP, higher American Society of Anesthesiologists (ASA) grades and older age[87]. However, in severe ABP, there is no evidence supporting early surgery. In a retrospective analysis, patients who received CCY six weeks after ABP onset had a better outcome than patients with earlier surgery[88] while another retrospective analysis in necrotizing ABP without peripancreatic fluid collection (PFC) revealed that CCY is best performed within eight weeks after discharge[80]. As appropriately designed studies in severe ABP are missing, postponing surgery until the pancreatitis resolves (i.e., no evidence of relevant PFC) appears to be a feasible approach [15,89] (Fig. 2).

5. Management of SAP complications

Local and vascular complications during or after an episode of SAP often necessitate endoscopic, percutaneous and/or angiographic intervention, and on rare occasions, even surgery (Table 6). Complications are mainly depicted by contrast-enhanced CT.

5.1. Local complications

Acute PFC (APFC) and acute necrotic collections (ANC) may develop early after symptom onset (typically 7–10 days) while pancreatic pseudocyst (PP) and walled-off necrosis (WON) usually develop later [1].

In terms of interventions the so-called "step-up approach" is well accepted [90–93]. The rule of thumb is "delay, drain, debride" emphasizing that interventions, if possible, should not be performed early and should be performed in the least invasive manner. APFC are usually self-limiting and do not require drainage[94]. PP also frequently resolve spontaneously (especially diameter <60 mm)[95]. However, mature PP may require drainage if they are symptomatic (e.g., obstructive symptoms) or cause complications such as cholestasis, infection or bleeding. Contrast-enhanced CT or MRI helps to confirm the maturity of the PP wall, the approach (e.g. proximity to the GI tract), surrounding vascular structures (e.g., pseudoaneurysms) and signs of disconnected pancreatic duct syndrome (DPDS) [96,97]. MRI is more diagnostic than CT but associated with higher costs and increased transportation time in patients with SAP [96,98]. EUS may be used as an (invasive) alternative that can be performed at the bedside on the ICU. Draining PP should be primarily attempted endoscopically, typically transmurally by EUS[99]. When a PP communicates with the main pancreatic duct (MPD) or when there is an evident MPD stricture, ERCP-guided transpapillary stenting of the MPD can be discussed[100]. However, additional transpapillary stenting after EUS-guided drainage was not beneficial in a retrospective study[101]. In case of PP-induced cholestasis, ERCP-guided biliary stenting should be combined with EUS-guided PP drainage. If EUS-guided drainage is not possible or not sufficient (e.g., PP extending into the pelvis), percutaneous approaches (ultrasound- or CT-guided) are possible alternatives[102] while surgical approaches usually remain the last resort [99,103,104]. Recent studies revealed that EUS-guided PFC drainage is, compared to percutaneous drainage, associated with higher clinical success, lower morbidity and mortality (e.g., less reinterventions, shorter hospital stay), higher patient comfort (e.g., no need of external drain) and lower risk of pancreato-cutaneous fistula formation (more details in the following chapter) [105–109]. PP usually resolve 4–6 weeks after endoscopic stent placement. In case of complete resolution and when there are no signs of DPDS, the stents are removed endoscopically. Otherwise, LAMS are replaced with PS. Specifics on ANC and WON management are discussed in the following chapter (Fig. 3).

Table 6
Common complications after severe acute pancreatitis and their typical onset, diagnostic approach and interventional management.

Complication		Onset	Diagnostic approach	Interventional management
Local	**Acute peripancreatic fluid collections (APFC)**	Early (typically 1–2 wk)	US > CT (alt.: MRI)	- Usually self-limiting. - When complicated, discuss EUS-guided vs. percutaneous drainage.
	Acute necrotic collections (ANC)	Early (typically after day 7–10)	CT (alt.: MRI) > US	- Empiric AIT with pancreatic penetration - Discuss no intervention vs. early or late intervention (prefer waiting in clinical stability) - Discuss mode of intervention (EUS > percutaneous > surgical)
	Pancreatic pseudocyst (PP)	Later (>3–4 wk)	CT (alt.: MRI) > US (discuss MRCP for interventional planning or primary EUS for ICU patients difficult to transport)	- Drain if symptomatic or causing complications. - Mode of intervention: Endoscopy (EUS, alternatively ERCP) > percutaneous > surgical - Non-endoscopic approach reserved for PP not amenable to endoscopy.
	Walled-off necrosis (WON)	Later (>3–4 wk)	CT (alt.: MRI) > US (discuss MRCP for interventional planning or primary EUS for ICU patients difficult to transport)	- Discuss indication of drainage (typically infected necrosis). - Mode of intervention: EUS > percutaneous > surgical. - Evaluate need of consecutive on-demand necrosectomy (alternatively: upfront necrosectomy). - In large necroses, discuss combined necrosectomy using luminal and percutaneous (VARD) approach. - Non-endoscopic approach reserved for PP not amenable to endoscopy (extrapancreatic necrosis)
Vascular	**Splanchnic vein thrombosis**	Early (<4 wk)	CT or MRI > US	- Discuss anticoagulation (stronger indication with more extensive thrombosis). - Discuss angiography in case of severe complications.
	Pseudoaneurysm	Early and late	CT or MRI	- Angiographic coiling.
	Abdominal compartment syndrome	Early (<4 wk)	IAP measurement (typically indirectly via urinary bladder catheter)	- Conservative measures of reducing IAP and according adaptation of MAP and PEEP. - Discuss decompressive laparotomy early.

The most common complications with the typically preferred diagnostic approach as well as the typically preferred management measures and their tendential prioritization are given. The use of surgical approaches is only mentioned in instances where they do not represent the last resort.
Abbreviations: AIT, anti-infective treatment; alt., alternatively; CT, computed tomography; EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; IAP, intraabdominal pressure; MAP; mean arterial pressure; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PEEP, positive end-expiratory pressure; VARD, video-assisted retroperitoneal drainage; wk, week.

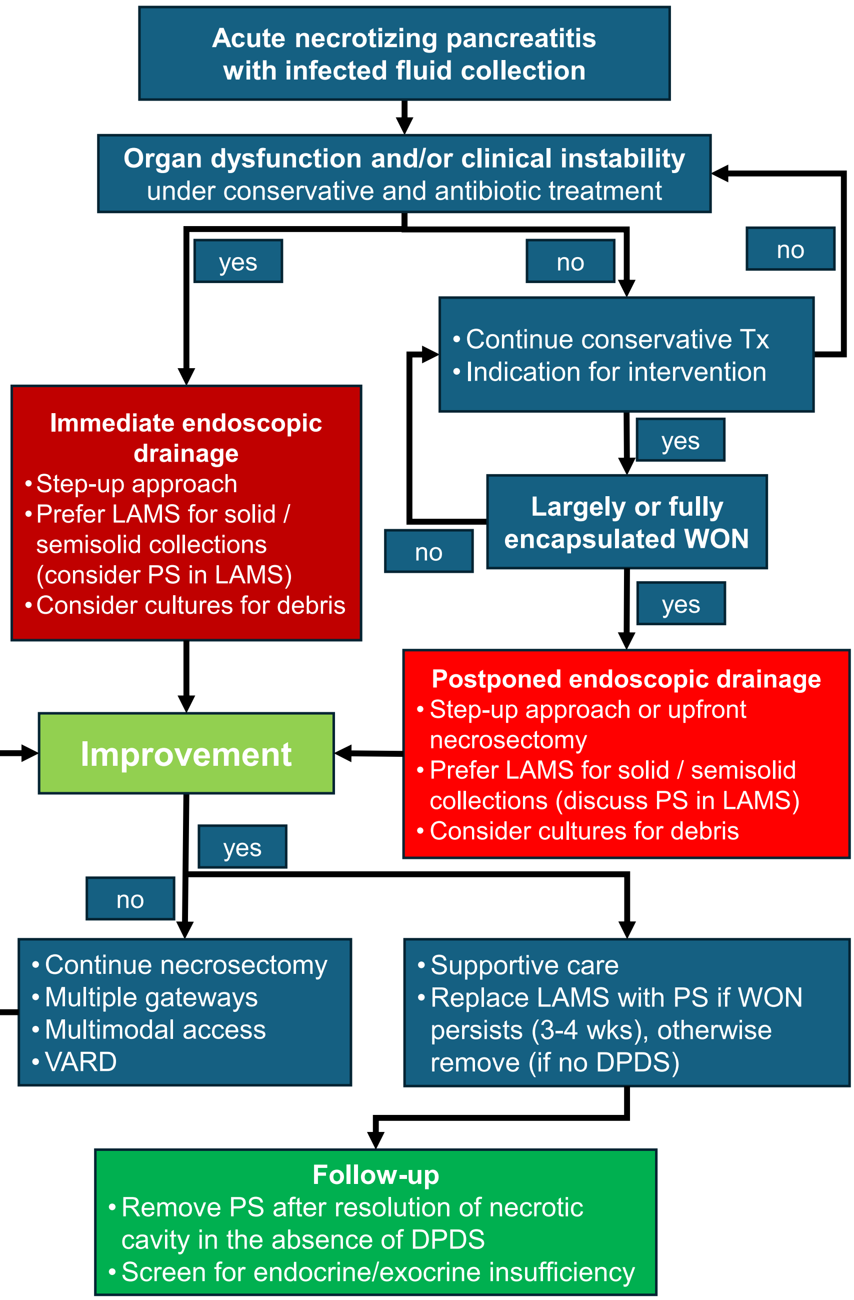

Fig. 3. Interventional management of acute necrotizing pancreatitis.
The typical interventional measures of acute necrotizing pancreatitis are depicted in form of a clinical-decision based algorithm. Ideally, the decisions should be made in a multidisciplinary setting. Abbreviations: DPDS, disconnected pancreatic duct syndrome; LAMS, lumen-apposing metal stent; PS, plastic stent (typically double-pigtail stents); Tx, treatment; VARD, video-assisted retroperitoneal drainage; WON, walled-off necrosis.

5.2. Vascular complications

Thrombosis can affect the portal, splenic, and/or mesenteric veins in up to 24% of cases[110]. While effective treatment of AP may lead to spontaneous resolution of the thrombosis, the impact of anticoagulation is unclear[111]. Given the scarce evidence, anticoagulation in more extensive thrombosis may be discussed. Chronic thrombosis can result in collateralization and sequelae of (left-sided) portal hypertension [112, 113]. In case of severe complications of thrombosis, multidisciplinary discussion regarding angiographic intervention should occur [111,114].

Pseudoaneurysms of peripancreatic vessels occur less commonly (but as many as 6.4% in necrotizing AP[115]) and can result in life-threatening hemorrhage. The primary treatment approach is angiographic coil embolization.

6. Management of acute necrotizing pancreatitis (ANP)

6.1. Approach to ANP

The interventional management of pancreatic and peripancreatic necrosis has significantly evolved after the demonstration of the feasibility of an endoscopic transgastric necrosectomy in 2009[116]. The PANTER trial[90] showed that open surgery was inferior to a surgical step-up approach with percutaneous drainage first followed by on-demand video-assisted retroperitoneal drainage (VARD) and necrosectomy: Risk of major complications or death was reduced in the step-up approach group (69% vs. 40%). Encouraged by these results, the TENSION trial[92] compared this surgical minimally invasive approach with an endoscopic step-up approach including an EUS-guided

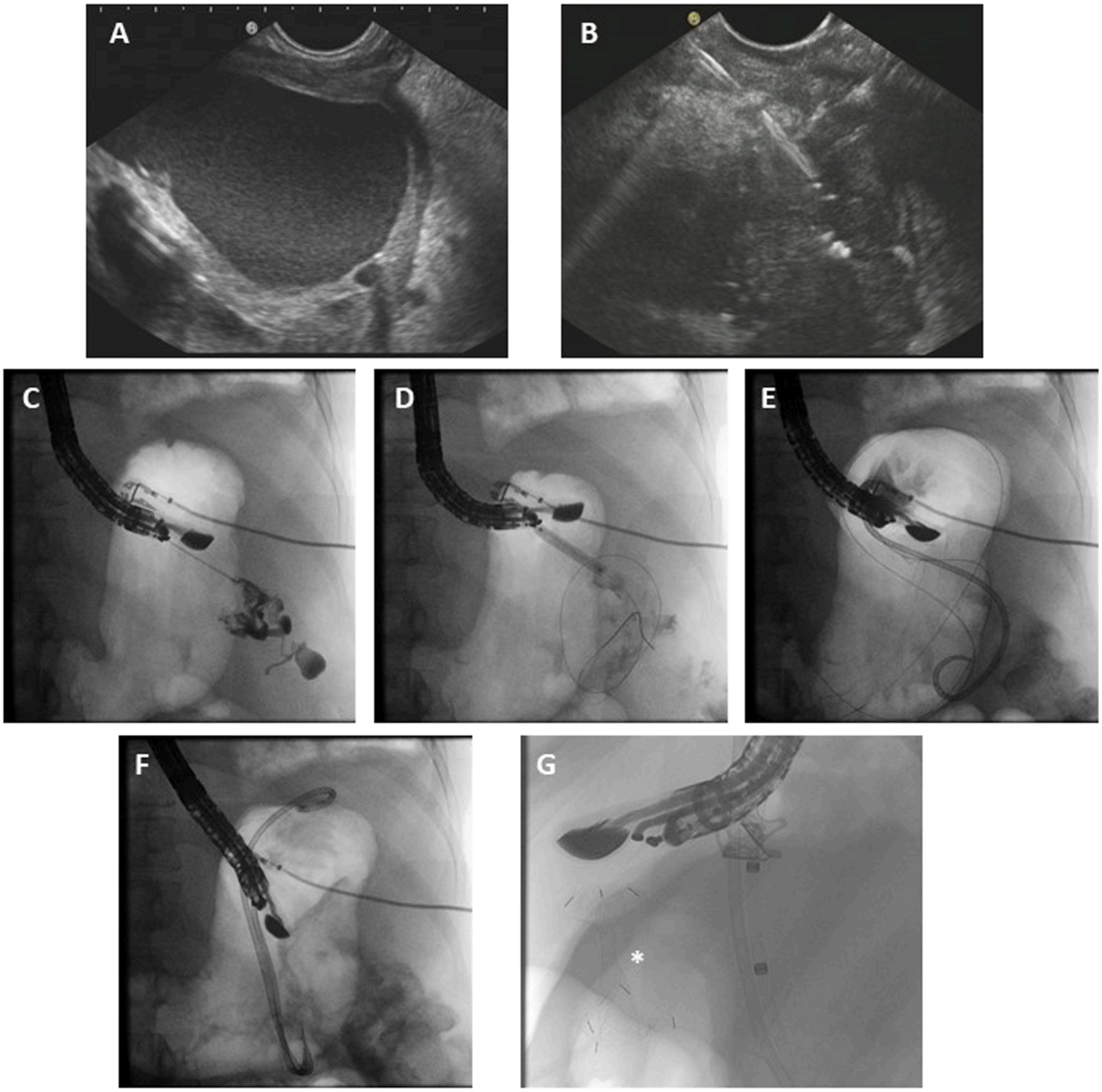

Fig. 4. Endoscopic transmural drainage of a pancreatic fluid collection.
Pancreatic fluid collections (PFC) can be drained endoscopically either using double-pigtail plastic stents or lumen-apposing metal stents (LAMS) that connect the gastric lumen with the PFC. This example shows the technique of transgastric drainage using two double pigtail stents. A) View of a walled-off necrosis (WON) with a longitudinal endosonography (EUS) scanner. B) EUS-guided puncture of the WON with a 19 G needle. C-D) Fluoroscopic view of the puncture: First, contrast fluid is applied through the needle into the WON to verify the successful transmural access to the WON. Next, a guidewire is inserted through the needle into the WON (C). Next, a dilation balloon is inserted over the guidewire into the WON to dilate the transmural access (D). Here, a sequential dilation (first 4 mm with a smaller dilation balloon, then dilation up to 18 mm with a larger dilation balloon) was used. E-F) Two double-pigtail plastic stents are inserted over the guidewire through the dilated access into the WON. G) Adjacent to the new transmural drainage is a LAMS (marked with "*") that connects another WON, that is not connected with the WON that was drained using the plastic stents. This exemplifies that sometimes multi-site endoscopic drainage is necessary for extensive necrotizing pancreatitis.

transluminal drainage followed by an on-demand endoscopic necrosectomy: While major complications or death did not differ, the rate of pancreatic fistula (5% vs. 32%) and hospital stay (53 vs. 69 days) favoured the endoscopic approach. These results were also confirmed by the long-term results of this trial after seven years of randomization (ExTENSION[93]) leading to the implementation of the endoscopic step-up approach as standard intervention for infected necrotizing pancreatitis by several guidelines [67,117]. Further studies highlighted the benefits of the endoscopic approach with regard to major complications, costs and quality of life [118,119]. Despite these convincing data, there are still considerations for surgery including failure of endoscopic or percutaneous interventions as well as emergency conditions such as ACS.

The treatment of extrapancreatic necrosis without communication to a transluminal access may require a (multisite) transabdominal drainage with a large-diameter drain followed by dilations and transabdominal necrosectomy. The necrosectomy may be facilitated by endoscopic view.

6.2. Timing of interventions

Usually, it is recommended to wait until an infected pancreatic or peripancreatic necrosis has become encapsulated (WON) (Fig. 2) [3]. This encapsulation often takes 3–4 weeks to develop but a clinical deterioration with multiorgan dysfunction will often require intervention if conservative treatment fails. The decision for or against an interventional treatment, in particular when an encapsulation of the necrosis has not fully developed, should be based on a multidisciplinary team including gastroenterologists, endoscopists, intensivists, surgeons

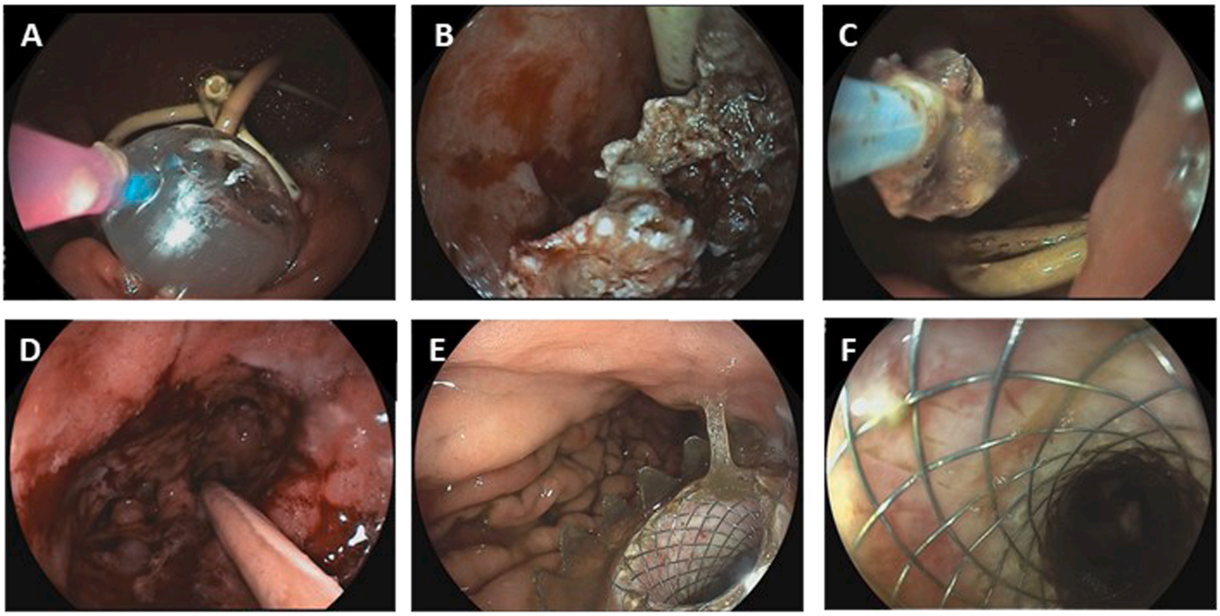

Fig. 5. Endoscopic transmural necrosectomy of a pancreatic walled-off necrosis.
Walled-off necroses (WON) as a sequelae of necrotizing pancreatitis can be drained endoscopically through the stomach or the duodenum. After the transmural access is secured, the WON can be entered with the endoscope and multiple tools can be inserted through the endoscope's working chancel into the WON to perform necrosectomy. A). Transgastric drainage of a WON with 3 double-pigtail plastic stents. The access is dilated with a dilation balloon to allow entrance with the endoscope into the WON. B) Necrotic material in the WON. C) Removal of necrotic material with snares (that are usually used for endoscopic polypectomy). Other tools may also be used. D) Clearance of the wound from necrotic material. E) Alternative approach to a WON with a lumen-apposing metal stent (LAMS). F) a LAMS allows intubation of the WON with the endoscope without prior dilation.

and radiologists. In general, indication for intervention are infected necrosis or symptomatic collections (see above). The POINTER trial [120] compared immediate endoscopic drainage (followed by on-demand necrosectomy) with postponed drainage after largely or fully encapsulation of the necrosis or clinical deterioration or lack of improvement: While complications or death did not differ, there were more interventions (4.4 vs. 2.6) in the immediate group. Interestingly, 39% in the postponed group did not require endoscopic intervention and could be treated conservatively with antibiotics although there was indication for intervention at randomization. Hence, immediate intervention in clinically stable patients is not recommended (Fig. 3). The DESTIN trial[121] compared endoscopic upfront necrosectomy (EUS-guided drainage with a lumen-apposing metal stent (LAMS) followed by same-session necrosectomy) with the endoscopic step-up approach (LAMS first and additional drainage or necrosectomy after 72 h if there was no clinical improvement): While mortality or disease- and procedure-related adverse events were comparable, the number of interventions was lower in the upfront group (IQR 0–1 compared to IQR 1–4). Thus, the upfront necrosectomy approach is a feasible alternative to the step-up approach in stabilized ANP.

6.3. Techniques of endoscopic drainage

Several technical improvements of the endoscopic approach have been made. Classically, a transluminal drainage was performed by an EUS-guided fine-needle puncture, guidewire-insertion, dilation and/or cystotome electrocauterization and implementation of at least two double-pigtail PS under fluoroscopic guidance (Fig. 4). LAMS with an electrocautery device for direct EUS-guided puncture and stent insertion simplified and accelerated drainage (Figs. 4 and 5). After drainage (and possibly dilation of the transmural tract into the WON), the endoscope is intubated into the necrosis and multiple tools are used to perform necrosectomy.

While single-center RCTs or retrospective cohort studies indicated a superiority of LAMS in treatment efficacy [122,123], another RCT showed no difference in number of procedures, treatment success or adverse events[124]. Although procedure time was shorter with LAMS (15 vs. 40 min), there was a remarkable number of bleeding events and stent overgrowth if the LAMS was placed for more than three weeks. This observation led to the recommendation to remove a LAMS after 3–4 weeks (Fig. 3). Additional RCTs during the recent years [109,125] confirmed these results and showed that the use of LAMS, compared to double-pigtail PS, did not reduce the need for necrosectomy[126]. Additional double-pigtail PS through the LAMS prevent LAMS occlusion and secondary infection but do not reduce bleeding risk [127,128]. Therefore, LAMS is equal compared to PS regarding efficacy and complications when the LAMS is removed not later than 3–4 weeks. However, it should be taken into consideration that procedure time and complexity is reduced and a LAMS can be placed without fluoroscopy, e.g. as bedside intervention in the ICU. Moreover, a LAMS should be preferred if additional necrosectomies are foreseeable (solid or semisolid necrotic tissue) as this large-diameter access to the necrotic cavity facilitates the removal of debris (Fig. 5).

After transmural endoscopic drainage, one RCT suggested leaving double-pigtail PS in situ as it appeared to lower the risk of recurrent PFC without any long-term complications[129] while another RCT did not show a benefit of PS placement after LAMS removal[130]. A recent meta-analysis favoured leaving long-term PS in situ[131].

Unanswered questions include the use of multiple transluminal gateways[132] or multimodal access (transluminal and percutaneous) [133], the need of a complete or partial necrosectomy, the use of hydrogen peroxide[134] or proton pump inhibitors[135], endoscopic vacuum therapy[136] or a rotating resection and suction device[137] as well as cost-effectiveness of LAMS vs. PS therapy [138].

Authorship statement

Conceptualization: KH, AK
Drafting of the manuscript: all authors
Critical revision of the manuscript for important intellectual content: all authors

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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