Advances in acute pancreatitis

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Purpose of review
With a potentially life-threatening course, acute pancreatitis (AP) is one of the most common gastrointestinal diseases requiring hospitalization and often necessitating intensive care. Based on recent insights and recommendations, this review provides an overview on clinical management of AP patients with a focus on intensive care unit care.

Recent findings
Possible benefits of percutaneous paracentesis and/or drainage on outcome or inflammation have been further explored. Combined opioid and epidural analgesia for pain management might be a valuable alternative for pain management. Very recent international guidelines now agree on a step-up approach for the management of acute necrotizing pancreatitis favoring a minimally invasive approach with either endoscopic or percutaneous drainage first. Studies for the best timing of these interventions are ongoing. In spite of a better understanding of pathophysiological mechanisms mediating AP, specific treatments are still awaited.

Summary
New evidence and recent international consensus direct the current management of AP toward a tailored, multidisciplinary and less invasive therapy with complementary roles for hepatologists, intensivists, radiologists, and surgeons.

Keywords
intensive care unit management, severe acute pancreatitis, step-up approach

INTRODUCTION

Acute pancreatitis (AP) is a possibly life-threatening and common gastrointestinal disease. Global estimates of incidence for AP are 34 per 100,000, with an increasing incidence [1,2]. AP causes local and systemic inflammation that varies in clinical severity. In total, 20% of the patients will develop moderate or severe acute pancreatitis (SAP) that can lead to necrosis of the pancreatic tissue and/or (multiple) organ failure (MOF) with a mortality rate up to 30% [3,4]. Efforts continue to unravel inflammatory pathways and recent clinical studies have focused on the role of percutaneous catheter drainage (PCD) and epidural analgesia. Based on new insights and treatment options for infected pancreatic necrosis recent guidelines uniformly agree on a multidisciplinary step-up approach. This review will set out the common thread for clinical management of AP focusing on intensive care management for SAP, whilst highlighting recent novelties.

ETIOLOGY

In Western countries the most frequent etiology of AP is biliary sludge or gallstones (40–50%), followed by alcohol (20%) [5,6]. Other causes like hypertriglyceridemia, endoscopic retrograde cholangiopancreaticography (ERCP), medication, hypercalcemia, surgery, and trauma are far less frequent. Genetic disorders (SPINK or CFTR-gene) are rare and mostly diagnosed in childhood and in essence represent a facilitating condition to AP rather than an etiologic driver [6]. Etiology of 10–25% of all AP remains unknown [7▪▪].

PATHOPHYSIOLOGY

The events central to the pathogenesis of AP are reviewed in depth by Lee *et al.* and include pathological calcium signaling, mitochondrial

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KEY POINTS

- Adequate fluid resuscitation, analgesia and nutrition remain cornerstones in the management of acute pancreatitis.
- A conservative strategy in patients with predicted severe acute gallstone pancreatitis is preferred over endoscopic intervention with early ERCP only in patients with cholangitis or persistent or evolving (obstructive) cholestasis.
- In severe acute pancreatitis earlier percutaneous paracentesis or drainage of fluid collections might improve outcome.
- There is international consensus for a step-up approach for the management of acute necrotizing pancreatitis favoring a minimally invasive approach with either endoscopic or percutaneous drainage first.

dysfunction, premature trypsinogen activation, endoplasmatic reticulum stress, impaired autophagy, and an impaired unfolded protein response [7▪▪]. These (sub)cellular events can be triggered by common acinar cell toxins like bile acids, alcohol, or nicotine [6]. Intraductal injury, like trauma or ERCP, causing increased intraductal pressure due to ductal obstruction, acidification, or ductal cell exposure to bile acids can indirectly trigger the inflammatory cascade [7▪▪,8]. Regardless of etiology, autodigestion and inflammation can lead to necrosis of pancreatic tissue. Immunological amplification of the initial inflammation is due to a generalized cytokine-mediated hyperinflammatory response [8]. Higher serum levels of tumor necrosis factor and interleukin-6, inducing more lymphocyte activation, are associated with disease severity and distant organ dysfunction [9,10]. Activated macrophages and monocytes have a central role in worsening local and systemic inflammation [7▪▪].

The understanding of these mechanisms and immunological responses offers possibilities for future treatments. Ongoing or recent experimental and clinical studies, interfering directly with one or more of these mechanisms, include statins, tocilizumab, lactated Ringer's solution, pentoxifylline, orlistat, and emodin [7▪▪,11–15]. However, these trials have either been negative (pentoxifylline) [13] or need clinical confirmation (e.g., tocilizumab) before introduction into clinical practice [11,12, 14,15].

DIAGNOSIS

Based on the 2012 revised Atlanta Classification, AP is defined as the presence of at least two of the three following criteria: (1) abdominal pain consistent with pancreatitis, (2) serum amylase and/or lipase of at least three times the upper limit of normal values or (3) imaging findings consistent with AP (ultrasound, contrast-enhanced computed tomography (CECT)) [16]. When the clinical and laboratory findings are clearly present, additional imaging with a CECT at index presentation is not required nor instructive.

Prognostication

Assessment of severity of disease is a critical step in the management of AP. Identifying patients at high risk for complications is valuable for the proper level of monitoring (Intensive Care Unit (ICU) versus non-ICU) and prognostication of mortality. Mortality in case of SAP is at least 10 times higher than in mild AP (10–30% versus <1%) [7▪▪,16].

Severity of AP is classified as (1) mild, when no local or systemic complication is present or (2) moderate in case of local (e.g., pancreatic fluid collections) or systemic (e.g., exacerbation of chronic disease) complications or transient organ failure (≤48 h) or (3) severe, in case of persistent organ failure (>48 h) [16].

Several scoring systems, such as the Acute Physiology and Chronic Health Evaluation-II score, the Ranson score, the Glasgow/Imrie score, bedside index of severity of acute pancreatitis and SIRS criteria (systemic inflammatory response defined as at least 2 of the following criteria: (1) temperature $< 36\,^{\circ}C/96.8\,^{\circ}F$ or $> 38\,^{\circ}C/100.4\,^{\circ}F$, (2) heart rate >90/min, (3) respiratory rate > 20/min and (4) white blood cells $> 4 \times 10^9$/L (>4 K/mm^3) or $> 12 \times 10^9$/L (>12 K/mm^3) or 10% bands), have been developed combining clinical and laboratory findings for the prognostication of a severe disease course. The CT Severity Index uses radiological parameters to determine AP severity, ranging from 0 to 10, with an associated mortality rate for each predefined interval [17]. Comparison of the clinical scoring systems demonstrates a comparable predictive value and accuracy of all these systems. Therefore, the International Association of Pancreatology and American Pancreatic Association (IAP/APA) guideline recommends using persistent SIRS (>48 h) because of its feasibility and association with MOF and mortality [4,18]. Persistent SIRS is a key predictor of mortality in SAP (25% mortality versus 8% mortality with transient SIRS) [15]. Patients should always be referred for ICU management in case of SAP as defined by the Revised Atlanta Classification or in case of AP with one or more critical clinical indicators as defined by the Society of Critical Care Medicine (Table 1) [19▪,20].

Table 1. Indication for admission to an intensive care unit in acute pancreatitis following the guidelines of the Society of Critical Care Medicine or Revised Atlanta Classification

Society of Critical Care Medicine	Revised Atlanta Classification
1. Pulse < 40 or > 150 beats per minute	Persistent SIRS > 48 h (1) temperature < 36 °C/96.8 °F or > 38 °C/100.4 °F, (2) heart rate >90/min, (3) respiratory rate > 20/min, (4) white blood cells > 4×10^9/L (>4 K/mm^3) or > 12×10^9/L (>12 K/mm^3) or 10% bands
2. Systolic arterial pressure < 80 mmHg (<10.7 kPa) Or Mean arterial pressure < 60 mmHg (<8.0 kPa) Or Diastolic arterial pressure > 120 mmHg (>16.0 kPa)	
3. Respiratory rate > 35 breaths/min	
4. Serum Sodium < 110 mmol/L or > 170 mmol/L	
5. Serum Potassium < 2.0 mmol/L or > 7.0 mmol/L	
6. PaO_2 < 50 mmHg (6.7 kPa)	
7. pH < 7.1 or > 7.7	
8. Serum glucose > 800 mg/dL (>44 mmol/L)	
9. Serum calcium > 15 mg/dL (3.75 mmol/L)	
10. Anuria	
11. Coma	

SIRS, Systemic Inflammatory Response Syndrome.

Imaging

Based on the 2019 World Society of Emergency Surgery guidelines, an abdominal ultrasound should suffice on admission to determine the etiology of AP [21▪▪]. In case diagnostic doubt (like f.e. due intestinal ischemia) remains an additional CT can be performed. CECT or magnetic resonance imaging have no place in the initial work-up for AP. Only magnetic resonance cholangiopancreaticography (MRCP) or Endoscopic Ultrasound (EUS) may be considered to screen for occult common bile duct stones, sludge, or deformities in patients with AP of unknown origin. EUS, if available, is preferred since it diagnostically outperforms MRCP [22].

EARLY INTENSIVE CARE MANAGEMENT (≤ 72–96 h)

There is no curative therapy for AP. Early interventions aim at (1) monitoring vital organ function, (2) supportive therapy with fluid resuscitation, analgesia, and nutrition, and (3) screening for possible complications.

Adequate fluid resuscitation is crucial since SAP leads to third space losses of fluid due to local and systemic inflammation that may result in hypovolemia, hypoperfusion, and ultimately in MOF. Only few randomized controlled trials (RCT) have been conducted assessing optimal fluid resuscitation. Due to an increased incidence of acute kidney injury (AKI) and possibly increased mortality, colloids are to be avoided in critically ill patients. In 40 patients, Wu *et al.* showed a significant reduction in SIRS criteria and in C-reactive protein using Ringer's Lactate in comparison to saline [15]. Although this advantage of Ringer's lactate or other balanced fluids has not been reproduced in large RCTs, the IAP/APA guideline recommends balanced electrolyte solutions in this setting. The amount of fluid administration should be goal-directed, combining regular assessment of intravascular volume with monitoring of several parameters indicative of hypoperfusion (i.e., 5–10 ml/kg/h initially until resuscitation goals have been reached) [4]. An adequate fluid status meets the following targets: (1) heart rate < 120/min, (2) mean arterial pressure between 64 and 85 mmHg (3) a urinary output of 0.5–1 ml/kg/h (4) stable hematocrit ranging between 33 and 44% and (5) stable blood urea nitrogen and creatinine levels [4].

Analgesia is another cornerstone of the AP management since pain is the predominant symptom. Several RCTs comparing different types of analgesia have been conducted, but due to their poor quality the IAP/APA guideline recommends to manage pain following local state-of-the-art pain protocols [4,23–27]. Recently, the focus has pivoted from opioids only to a combination of opioids and epidural anesthesia. This multimodal approach may be associated

with a lower mortality due to beneficial effects on pancreatic blood flow and inflammation with an RCT ongoing [28,29].

A third key issue in the AP management is enteral nutrition. Enteral nutrition significantly reduces infection, organ failure rates, and mortality [30]. A multicenter RCT demonstrated that early enteral tube feeding (<24 h after admission) was not better than late oral feeding (>72 h after admission) [31]. Tube feeding should therefore be limited to those SAP patients with an insufficient oral caloric intake after 3–5 days [32]. No significant differences in outcome have been described between nasogastric and nasojejunal tube feeding [33]. Parenteral nutrition is second-line therapy when after 7 days oral or tube feeding is not tolerated or insufficient [4].

Development of AKI, abdominal compartment syndrome (ACS), or acute respiratory distress syndrome (ARDS) are three major complications to be monitored for. AKI prevention and treatment consists of adequate fluid resuscitation and when necessary initiation of renal replacement therapy [15,34]. ACS is defined as a sustained intra-abdominal pressure (IAP) > 20 mmHg associated with new onset organ failure. ACS in this setting has a high mortality of 49% (range 25%-83%), making IAP monitoring imperative [35]. In cases where abdominal hypertension (AH) (IAP > 12 mmHg) evolves to ACS, decompressive measures (medical/surgical) should be considered [4]. Recently, two research groups showed beneficial effects of PCD of abdominal fluid in case of AH or pancreatic fluid collections [36▪▪,37▪]. Moreover, a reduction of IAP in patients with AH by >40% at 48 h after PCD was associated with better survival (63.3% versus 36.7%, p=0.006) [36▪▪].

In case of ARDS, treatment does not differ from that of ARDS due to other causes. Veno-venous extracorporeal membrane oxygenation in SAP may rarely serve as a possible add-on therapy for ARDS when ARDS-specific mechanical ventilation fails [8,38,39].

Early biliary treatment with ERCP (±EUS) within the first 24 h after admission is only indicated in case of biliary pancreatitis with concomitant cholangitis [4,40]. In case of the latter antibiotic treatment with broad-spectrum antibiotics with good biliary penetrance (e.g., piperacillin-tazobactam, quinolones, meropenem, or cephalosporines) should be associated [41,42]. The use of (early) ERCP with EUS in predicted severe biliary disease remains controversial. In a systematic review De Lisi *et al.* concluded that an EUS-first strategy (EUS only followed by ERCP in case of choledocholithiasis) versus an ERCP-only strategy avoided ERCP in 71.2% of the cases [43]. The recent APEC-trial in patients with predicted severe gallstone pancreatitis without cholangitis comparing urgent ERCP with sphincterotomy to conservative treatment showed no significant reduction in major complications or mortality rate [44▪▪]. Therefore, a conservative strategy in patients with predicted severe acute gallstone pancreatitis is preferred over endoscopic intervention with early ERCP only in patients with cholangitis or persistent or evolving (obstructive) cholestasis.

LATE INTENSIVE CARE MANAGEMENT (>96 h)

Screening for (peri-)pancreatic collections and infected necrosis

Complications of AP as defined in the 2012 Atlanta Classifications can be divided in edematous pancreatitis and necrotizing pancreatitis [16]. The latter is subdivided in parenchymal and peripancreatic necrosis, but in most cases a combination is seen. CECT within the first 3–5 days is only indicated when bleeding, ischemia, or perforation is suspected and only becomes reliable and of utmost importance for the evaluation of the extent of (peri)-pancreatic necrosis and associated complications after 5 days [32]. Peripancreatic collections are referred to as 'acute pancreatic fluid collections' or 'acute necrotizing collections (ANC)' [16,45▪]. When ANC get encapsulated after 4–6 weeks it evolves to a walled-off necrosis (WON). Encapsulated collections with mere fluid are termed acute pseudocysts but are rare in comparison to WONs. WON can remain sterile or become infected. Infected necrotizing pancreatitis occurs in approximately one-third of the patients and can be diagnosed by (1) gas formation in the necrotic collection on imaging, (2) positive gram stain or culture from (percutaneous) fine-needle aspiration (FNAC) of the necrotic collection or (3) clinical suspicion [45▪]. However, routine FNAC is not recommended due to high false positive rates [4,45▪].

Management of (peri-)pancreatic collections and infected necrosis

Acute pancreatic fluid collections without necrosis and/or pancreatic pseudocysts mostly resolve spontaneously, without any intervention. When ANC infection is proven or clinically highly suspected, broad-spectrum antibiotic treatment should be initiated. Carbapenems and quinolones have proven to penetrate the pancreatic tissue well, followed by cephalosporins and piperacillin-tazobactam [46,47,48▪]. Antibiotic prophylaxis to prevent infection is not recommended, neither are probiotics or selective

Table 2. Overview of the indications and timing for intervention in case of necrotizing pancreatitis following the International Association of Pancreatology and American Pancreatic Association (IAP/APA), the World Society of Emergency Surgery (WSES) and the American Gastroenterological Association (AGA) guidelines [4,21▪▪,49▪▪]

	IAP/APA guidelines (2013)	**WSES guidelines (2019)**	**AGA guidelines (2020)**
	Either radiological, endoscopic or surgical interventions	**Percutaneous or endoscopic interventions**	**Percutaneous intervention**
Indications for intervention in necrotizing pancreatitis	Clinical suspicion of, or documented, infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off In the absence of documented infection necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of AP, preferably when the necrosis has become walled-off. Less common: ACS Ongoing bleeding Ongoing gastric outlet, intestinal or biliary obstruction due to mass-effect of WON (i.e., arbitrarily > 4–8 weeks after onset of AP) Bowel ischemia In case of sterile necrotizing pancreatitis: Ongoing gastric outlet, intestinal or biliary obstruction due to mass-effect of WON (i.e., arbitrarily >4–8 weeks after onset of AP) Persistent symptoms (e.g., pain, malaise) in patients with WON without signs of infection (i.e., arbitrarily >8 weeks after onset of AP) Disconnected duct syndrome with persisting symptomatic (e.g., pain, obstruction) collection(s) without signs of infections (i.e., arbitrarily >8 weeks after onset of AP)	Clinical deterioration with signs or strong suspicion of infected necrotizing pancreatitis >4 weeks after onset: Ongoing organ failure without signs of infected necrosis Ongoing gastric outlet, biliary or intestinal obstruction due to a large WON collection Disconnected duct syndrome Symptomatic or growing pseudocyst >8 weeks after onset: Ongoing pain and/or discomfort	When endoscopic drainage is unavailable, unsuccessful or not technically feasible In case of necrosis extending into one or both paracolic gutters and/or into the pelvis In patients in the early phase of AP (<2–4 weeks) who have suspected or confirmed infected necrosis – without the presence of a walled-off collection – and are failing conservative medical management.
			Endoscopic intervention
			Central retrogastric collection Retrogastric collection with extension to the right of the mesenteric vessels Retrogastric collection with paracolic gutter extension, when percutaneous drainage fails.
		Surgical intervention	Surgical intervention
		As a continuum in a step-up approach after percutaneous/endoscopic procedure with the same indications ACS Acute ongoing bleeding when endovascular approach is unsuccessful Bowel ischemia or acute necrotizing cholecystitis during AP Bowel fistula extending into a peripancreatic collection	Infected or sterile pancreatic necrosis with persistent organ dysfunction or failure to thrive As a continuum in a step-up approach after percutaneous/endoscopic procedure with the same indications Drainage of pancreatic fistula in case of disconnected duct syndrome Large burden of necrosis, diffusely distributed throughout the abdomen
Timing for intervention	At least >4 weeks after presentation (if clinically possible)	At least >4 weeks after presentation (if clinically possible)	Percutaneous: < 2 weeks Endoscopic: < 4 weeks Surgery: ≥4 weeks

AP, acute pancreatitis; ACS, abdominal compartment syndrome; WON, walled-off necrosis.

gut decontamination [4,21▪▪]. Antifungal therapy may be necessary and should be based on clinical assessment and previous exposure or known colonization, favoring fluconazole followed by echinocandins [48▪].

More invasive interventions should be delayed, if possible, until the stage of WON [4,21▪▪]. Furthermore, the current guidelines advocate a step-up approach based on the PANTER trial as follows: (1) endoscopic or percutaneous drainage (E/PD), (2) minimal invasive/endoscopic necrosectomy and (3) open surgical necrosectomy [4,21▪▪,49▪▪,50]. E/PD is only followed by necrosectomy when clinically indicated. All indications for step-up following the IAP/APA and American Gastroenterological Association are listed in Table 2. The ongoing POINTER and TENSION trials examine the ideal timing for PD (delayed versus immediate) and compare a transluminal endoscopic versus a minimally invasive surgical step-up approach, respectively, in a RCT setting and results are awaited [51,52].

In general, guidelines recommend a multidisciplinary approach in a specialized referral center with intensivists, gastroenterologists, biliopancreatic endoscopists, (interventional) radiologists and pancreatic surgeons [4,21▪▪,49▪▪].

Disconnected pancreatic duct syndrome (DPDS, aka disconnected pancreatic tail syndrome) and vascular complications

DPDS is characterized by a loss of integrity of the pancreatic duct (mostly tail portion of the pancreas) following more centrally focused necrotizing pancreatitis of the body of the pancreas, occurring in about 40% of AP complicated with fluid/necrotic collections and resulting in abdominal pain or recurrent pancreatitis [32,49▪▪,53]. Diagnosis is best with (secretin-stimulated) MRCP and was traditionally treated surgically [49▪▪]. Recently, endoscopic ultrasonography-guided transgastric/enteric drainage procedures in conjunction with or without ERCP-assisted pancreatic duct stenting have emerged as an increasingly efficient and less invasive technique to manage this condition [54].

Vascular complications include venous thrombosis in about 15% of the patients with AP, usually resulting in recanalization. Anticoagulation in this setting remains controversial [45▪]. Pseudoaneurysms are rare and sometimes need to be embolized and/or stented [7▪▪,45▪,55].

Exocrine and endocrine insufficiency

Extensive pancreatic tissue necrosis can cause an important decline in both endocrine and/or exocrine pancreatic function [32]. In a recent systematic review and meta-analysis of patients with predominately SAP, the pooled prevalence of exocrine pancreatic insufficiency (EPI) was 62% and decreased to 35% after follow-up (39 follow-up studies with a follow-up ranging from 12 to 60 months, $I^2 = 92\%$) [56]. EPI prevalence doubled in SAP when compared to mild AP and was highest in patients with pancreatic necrosis and alcoholic etiology. Studies show one-third of the AP patients developing (pre)diabetes within 5 years of the index episode [57,58]. Awareness on these complications is important for clinical practice.

Prevention of recurrence

Recurrent AP will occur in 17–22% of AP patients and ~10–15% will develop chronic pancreatitis [59,60]. To reduce recurrence, elimination of known risk factors is important. Changes in life style patterns like alcohol abstinence, smoking cessation, and dietary measures should be advised [32,59,61]. In patients with biliary pancreatitis, cholecystectomy (CCE) will reduce the risk of recurrence, however, the optimal timing is still debated. Currently, international guidelines recommend a laparoscopic CCE during index admission for patients with mild AP or patients who only had an ERCP and sphincterotomy [4,21▪▪,49▪▪]. For patients with acute biliary pancreatitis complicated with peripancreatic fluid collections, the CCE should be delayed until the collections either resolve or, if still present after 6 weeks, when stabilized and inflammation has ceased [21▪▪,49▪▪].

CONCLUSION

Our understanding of inflammatory pathways involved in AP is improving continuously. A translation of this increased knowledge into better clinical outcomes is still awaited. Adequate fluid therapy, analgesia and nutrition remain cornerstones in the general ICU management. Recent guidelines uniformly recommend a multidisciplinary step-up approach for SAP using percutaneous, endoscopic and surgical interventions as a continuum of therapeutic options. Ongoing trials are expected to fine-tune the timing of these interventions.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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