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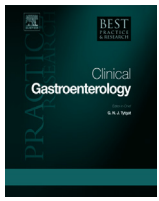

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Early management of acute pancreatitis

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A B S T R A C T

Acute pancreatitis is the most common gastro-intestinal indication for acute hospitalization and its incidence continues to rise. In severe pancreatitis, morbidity and mortality remains high and is mainly driven by organ failure and infectious complications. Early management strategies should aim to prevent or treat organ failure and to reduce infectious complications. This review addresses the management of acute pancreatitis in the first hours to days after onset of symptoms, including fluid therapy, nutrition and endoscopic retrograde cholangiography. This review also discusses the recently revised Atlanta classification which provides new uniform terminology, thereby facilitating communication regarding severity and complications of pancreatitis.

Abbreviations: ACS, abdominal compartment syndrome; CARS, compensatory anti-inflammatory response syndrome; CBD, common bile duct; CECT, contrast-enhanced computed tomography; ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; HES, hydroxyethyl starch; ICU, intensive care unit; IDUS, intraductal ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; SIRS, systemic inflammatory response syndrome.

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Introduction

Acute pancreatitis is the most common gastro-intestinal reason for acute hospitalization in the United States with annually more than 270,000 admissions and estimated costs of 2.6 billion dollars [1]. The incidence of acute pancreatitis continues to rise and the burden on patients and society is expected to increase even more [1–3].

Acute pancreatitis is an inflammatory process that is initiated by intra-acinar activation of proteolytic pancreatic enzymes, which ultimately leads to autodigestive injury of the pancreatic gland. Modulated by cytokines and other inflammatory mediators, intrapancreatic and extrapancreatic inflammation is generally accompanied by a systemic inflammatory response syndrome (SIRS).

Acute pancreatitis is associated with an overall mortality rate of up to 5% [1,4]. Approximately 15% of patients with pancreatitis develop pancreatic or extrapancreatic necrosis, which is associated with hospitalizations that can often last for several months [4]. These patients have a high risk of complications such as organ failure or infected necrosis with mortality rates of 35% and 20%, respectively [5].

Early management strategies (i.e. arbitrarily defined as within the first five days) in patients with acute pancreatitis are aimed at preventing or treating complications such as infections, organ failure and ultimately mortality.

Immediately after clinical presentation a comprehensive clinical work-up is mandatory and important decisions regarding management, including supportive care, need to be taken (Table 1). This review addresses the possibilities for management and early invasive interventions which might ameliorate the disease course and improve outcome in patients with acute pancreatitis.

Methods

A PubMed search was performed using the terms (pancreatitis (MeSH Terms)) AND (pancreatitis (Title/Abstract)) NOT (chronic (Title/Abstract) OR carcinoma (Title/Abstract) OR autoimmune (Title/Abstract)). A restriction in the search to articles in English, studies in human adults and a publishing date between May 2010 and May 2013, resulted in 672 hits. The titles were scanned manually and articles of interest regarding early management were reviewed. In addition, the evidence based guideline on the treatment of acute pancreatitis, established during the International Association of Pancreatology/American Pancreatic Association annual meeting in 2012, was reviewed. Relevant literature was extracted from the reference lists of the selected articles.

Diagnosis

The diagnosis of acute pancreatitis is made by fulfilling two of the three following criteria: (1) abdominal pain, (2) an elevated serum lipase or amylase (>3 times the upper limit of normal), (3)

Table 1
Key points early management in acute pancreatitis.

Diagnosis	• Acute pancreatitis; two out of three: ◦ Abdominal pain ◦ Elevated amylase/lipase >3 times upper limit of normal ◦ Characteristic findings on CT, MRI or ultrasound • Establish aetiology • Monitor and predict severity (limited accuracy)
Imaging	• Abdominal ultrasound • CT not routinely advised at admission, only after 4–5 days in case of lack of clinical improvement
Fluid therapy	• Balanced upon clinical response • 5–10 mg/kg/h (no specific recommendation for fluid type)
Bile duct management	• Cholangitis: emergency ERC • Predicted mild biliary pancreatitis: no ERC • Predicted severe biliary pancreatitis: no consensus about value ERC
Nutrition	• Predicted mild pancreatitis: on patients demand, early start • Predicted severe pancreatitis: no consensus on timing of nutrition

characteristic findings of acute pancreatitis on imaging, usually contrast-enhanced computed tomography (CECT) [6]. In most cases, acute pancreatitis is diagnosed by abdominal pain and an elevated serum lipase or amylase. In certain circumstances, for instance longer duration of complaints where serum amylase and lipase levels may have normalized, sedated patients or in case of suspected early complications, additional imaging is required. Characteristic findings of acute pancreatitis on CECT or magnetic resonance imaging (MRI), confirm the diagnosis [7–9]. As a CECT early in the disease course may underestimate the extent of pancreatic or extrapancreatic necrosis, and often does not result in a change in management, it should not be performed routinely at admission [7,10,11].

Key points diagnosis

- ➢ Acute pancreatitis, two out of three; (1) abdominal pain, (2) >3 times elevated serum lipase or amylase (3) characteristic findings of acute pancreatitis on imaging.
- ➢ CECT is not routinely advised at admission.

Clinical course

The initial phase of acute pancreatitis is characterized by pancreatic inflammation that usually presents as SIRS [12,13]. Approximately 30% of patients develop SIRS within 48 h after admission [13]. Persistent organ failure is the key determinant of mortality in acute pancreatitis and is associated with a mortality of 25–35% [5,13–15]. In theory, SIRS is followed by a compensatory anti-inflammatory response syndrome (CARS), a state of immune suppression, making patients more susceptible for infections including infection of pancreatic necrosis [16]. The mortality in the second phase of acute pancreatitis is mostly caused by infected necrotizing pancreatitis [15].

About 85% of patients with acute pancreatitis develop interstitial oedematous pancreatitis [4]. The inflammatory oedema of the pancreas usually resolves within one week [17]. Necrosis occurs in the approximately other 15% of patients, which can involve the pancreatic parenchyma, extrapancreatic tissues or both [6,18]. Extrapancreatic necrosis alone is associated with fewer complications as compared to solely parenchymal necrosis. However, once infection of extrapancreatic necrosis occurs, mortality rate is similar as for infected pancreatic parenchymal necrosis [19]. The recent revision of the Atlanta classification describes pancreatic and extrapancreatic collections in order to provide a consistent, worldwide classification in terminology. This description differentiates acute extrapancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis [6]. Table 2 provides definitions, according to the revisited Atlanta, of the morphological features in acute pancreatitis.

Key points clinical course

- ➢ Persistent organ failure is defined as >48 h, transient as ≤48 h.
- ➢ Persistent organ failure is the key determinant of mortality.
- ➢ Pancreatic necrosis can involve the pancreatic parenchyma, extrapancreatic tissues or both.

Predicting severity

Prognostic scoring systems have been developed to identify patients with a high risk of severe pancreatitis for three reasons. First, they may determine which patients need intensive monitoring

Table 2
Definitions in acute pancreatitis [6,116].

Interstitial oedematous pancreatitis	Inflammation of pancreatic parenchyma and extrapancreatic tissue, without necrosis
Necrotizing pancreatitis	Parenchymal and/or extrapancreatic necrosis
Severity	
Mild	No organ failure or local/systemic complications
Moderate	Transient organ failure or local/systemic complications
Severe	Persistent organ failure (>48 h)
Intra-abdominal hypertension	>12 mmHg, technique described in guideline [116]
Abdominal compartment syndrome	>20 mmHg and new organ failure
Collections	
Acute extrapancreatic fluid collection	Extrapancreatic fluid associated with interstitial oedematous pancreatitis
Pancreatic pseudocyst	Encapsulated collection of fluid without necrosis, after interstitial oedematous pancreatitis
Acute necrotic collection	Collection containing fluid and necrosis associated with necrotizing pancreatitis
Walled-off necrosis	Encapsulated collection in necrotizing pancreatitis

on high dependency units because of a high risk of organ failure. Second, the subgroup of patients can be selected in whom early, aggressive intervention is indicated. Third, they may be used to stratify patients in clinical trials with different (predicted) severities of acute pancreatitis [20].

The accuracy of the scoring systems, however, remains disappointing. In clinical practice their use is further limited by the complexity of many scoring systems. There are several scoring systems that are based on a combination of clinical and biochemical parameters (Acute Physiology and Chronic Health Evaluation (APACHE)-II, the Ranson score, Modified Glasgow or Imrie score, C-reactive protein, Bedside Index of Severity in Acute Pancreatitis (BISAP), Harmless Acute Pancreatitis Score (HAPS) and blood urea nitrogen (BUN)). A systematic review demonstrated that most prognostic variables and scoring systems have high negative predictive values, but low positive predictive values regarding positive predictive power [21]. In addition, CECT scoring systems can assess the extent of the morphological abnormalities. As they do not outperform clinical scoring systems with regard to prognosis, a CECT at admission solely for severity assessment is not recommended [11]. Recently a head-to-head comparison was performed on the accuracy of the scoring systems in predicting persistent organ failure [22]. Receiver operating characteristic analysis at admission showed modest results (0.62–0.84 in the training cohort and 0.57–0.74 in the validation cohort). Although the modified Glasgow score served as best predictor, the conclusion was drawn that the presently available scoring systems have reached their maximal performance and that combining clinical scoring systems does not further improve predictive value. To improve early management in patients with acute pancreatitis, there still remains a need for accurate markers to predict the disease course.

Simple laboratory values – such as BUN and creatinin – and more complex laboratory scoring systems have shown to have similar accuracies [22,23]. In line with their simplicity for clinical use, the upcoming IAP/APA guidelines recommend persistent SIRS (>48 h) as a marker to predict severity because of its easy utility and worldwide recognition, while awaiting more accurate scoring systems [13,24,25]. The fact that persistent organ failure is the key determinant of mortality in pancreatitis plays an important role in this recommendation.

The revised Atlanta classification has three groups of clinical severity: mild, moderate and severe pancreatitis. ‘Mild’ pancreatitis is characterized by no organ failure or extrapancreatic collections. ‘Moderate’ pancreatitis, has transient organ failure (≤48 h) or extrapancreatic collections. ‘Severe’ pancreatitis involves persistent organ failure (>48 h). Prospective studies are needed to identify the validity and clinical use of the classification and the first validation study has recently been published [26]. Some authors have suggested to divide clinical severity into four groups [27].

Key points predicting severity

- ➢ None of the available scoring systems for predicting severity is clearly superior, and new markers are needed.
- ➢ The revisited Atlanta classification defines mild, moderate and severe pancreatitis.

Aetiology

Although several factors are known to potentially cause acute pancreatitis, the exact pathogenesis remains unclear [28]. There is a large variation in aetiology of acute pancreatitis between countries. Most cases of acute pancreatitis are caused by biliary stones or sludge, followed by alcohol abuse [29,30]. The rise in incidence of acute pancreatitis has been attributed to either the increase of abdominal obesity – a risk factor for gallstones – ageing or an increase of alcohol consumption [2,30–32]. Less frequent causes of pancreatitis are hypercalcaemia, hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), medication and trauma.

The aetiology of pancreatitis should be determined on admission as this tailors management strategies. Medical history (gallstone disease, alcohol abuse, medication, metabolic syndromes), physical examination and biochemical tests (liver tests, calcium, triglycerides) help to differentiate between biliary and metabolic causes [33].

Diagnosing biliary pancreatitis in the early course of the disease may be difficult. The first challenge is to reliably ascertain whether common bile duct (CBD) stones are present. Unfortunately, clinical predictors of biliary obstruction (i.e. cholestatic liver enzymes) and radiologic findings have shown to be unreliable in predicting the presence of CBD stones in the early stages of biliary pancreatitis [34].

Elevations of biochemical markers, such as bilirubin, alkaline phosphatase, gamma-glutamyltransferase, alanine aminotranferase (ALAT) and aspartate aminotransferase suggest a biliary cause. However, about 15–20% of the patients with biliary pancreatitis manifest with normal liver function tests [35]. ALAT is thought to be the most useful biochemical marker in predicting a biliary origin in acute pancreatitis. An ALAT level of $>$150 IU/L (2.55 μkat/L, an approximately three-fold elevation) has been shown to have a positive predictive value of 88–100% in determining a biliary origin [36–38]. Within 48 h of hospital admission, an ALAT level of $>$80 IU/L (1.00 μkat/L, an approximately two-fold elevation) is also associated with a high probability (positive predictive value 79–100%) of biliary pancreatitis [33,39].

Abdominal ultrasound should be performed at admission to detect gallstones or sludge. The choice for this non-invasive imaging modality is often made because of its availability and low costs. Abdominal ultrasound has a high sensitivity for cholecystolithiasis, but has a low sensitivity (20%) for stones in the CBD in acute pancreatitis and can be troublesome in obese patients [34,40]. CECT is also not attractive as a test for CBD stones as sensitivity is 40% [40]. Finally, of the non-invasive imaging modalities, the result of a head-to-head comparison study of the ability of magnetic resonance cholangiopancreatography (MRCP) to detect choledocholithiasis in biliary pancreatitis was high, approximately 90% [40,41]. However, small gallstones ($<$5 mm) in the common bile duct can be easily missed on MRCP [42]. This is particularly relevant as especially small stones are known to cause biliary pancreatitis [43].

Of all imaging modalities, endoscopic ultrasound (EUS) is clearly superior in detecting choledocholithiasis, with a high sensitivity and specificity of 89–96% [36,44,45]. However, EUS has practical limitations because of its limited availability. The sensitivity of endoscopic retrograde cholangiography (ERC) is 90% [40]. In contrast to EUS, ERC has a 4–7% risk of developing complications, which can even be higher in patients with pancreatitis [46,47]. Based on these considerations it is clear that EUS and MRCP could play an important role in selecting patients for ERC. One study already showed that 71% of ERCs may be avoided using EUS as guidance [45]. Finally, intraductal ultrasonography (IDUS) has shown to be the best predictor for detecting choledocholithiasis with a sensitivity of 95% but obviously requires bile duct cannulation [40].

In about 10–15% of the cases the aetiology of pancreatitis remains unclear, although thorough investigation with IDUS, EUS or MRCP eventually reveals a biliary origin in a significant amount of presumed 'idiopathic cases' [48].

Key points aetiology

- ➢ Biliary stones or sludge are the most common cause of pancreatitis in most countries.
- ➢ An ALAT >150 IU/L (>2.55 μkat/L) is highly suggestive for a biliary cause.
- ➢ EUS or MRCP are modalities of choice to detect CBD stones.

Pain management

The predominant symptom of acute pancreatitis is abdominal pain. In addition to increasing patient comfort, alleviating pain moderates the physiological response to pain and immunological mechanisms. Intravenous opiates are usually necessary to control pain, though no evidence supports the use of a specific opiate [4,49]. Oxygen saturation should be monitored, as a side-effect of opiates is respiratory suppression.

Fluid therapy

In order to prevent intravascular volume depletion, hypoperfusion and organ failure, adequate fluid resuscitation is critical in the early management of acute pancreatitis to reduce complications and mortality [50,51]. In clinical practice, extensive fluid resuscitation is used as this is thought to maintain the microcirculation of the pancreas [52]. Recently, two randomized trials showed that too aggressive fluid therapy may result in higher mortality. The first trial compared infusion rates of 10–15 mg/kg/h with 5–10 mg/kg/h [53]. The second trial compared slow to rapid haemodilution aiming at a turning point of a haematocrit of 35% within 48 h [54]. Based on the available literature, it can be concluded that an infusion rate of 5–10 ml/kg/h seems appropriate, balanced upon clinical response (urine output and heart rate) [25]. Few studies have investigated the type of fluid that should be administered [55,56]. Recent data suggests that Ringer's lactate solution is superior to saline solution in preventing a SIRS [56]. Others suggest that a combination of normal saline, hydroxyethyl starch (HES) and glutamine is more efficient in resuscitation of severe pancreatitis by reducing SIRS [57]. In contrast, in a multicenter, blinded, randomized trial, patients with severe sepsis who were resuscitated with HES, had an increased risk of death and were more likely to require renal-replacement therapy, compared to those receiving Ringer's acetate [58]. A recent systematic review concluded that there is a lack of quality evidence on fluid therapy in acute pancreatitis [59]. In conclusion, fluid resuscitation is a cornerstone in the treatment of pancreatitis and should be balanced upon clinical response.

Key points fluid therapy and pain management

- ➢ An infusion rate of 5–10 ml/kg/h with response monitoring is appropriate for most patients.
- ➢ There is no clear superior type of fluid, more studies are needed.

Bile duct management

Especially small gallstones and sludge are associated with an increased risk of biliary pancreatitis [43]. The exact pathogenesis of biliary pancreatitis remains unknown [60]. Once biliary obstruction is thought to be present, decompression is thought to improve the disease course.

Since the introduction of ERC in the seventies as a diagnostic and therapeutic tool, it has become the standard treatment modality for patients with choledocholithiasis in biliary pancreatitis [61]. In order

to improve the outcome in biliary pancreatitis by decompression of the ampullary orifice and the bile duct, the effects of ERC have been investigated in experimental and clinical studies [62–65]. These studies suggest that a temporary biliary obstruction does not only initiate an attack of biliary pancreatitis, but also aggravates the disease course. Furthermore, post-mortem studies identified stones in the CBD of patients that died of necrotizing pancreatitis [66,67]. In the view of these findings, biliary decompression might be a potential life-saving intervention.

On the other hand, ERC plus endoscopic sphincterotomy is an invasive procedure associated with a complication rate of 8–10% and mortality rate of approximately 1% [68,69]. It is well known that in many patients CBD stones pass spontaneously in which case an ERC would be redundant [70,71].

In the past decades several randomized trials investigated the role of ERC in biliary pancreatitis. There is an undisputed indication for an urgent ERC in case of cholangitis [72,73]. Endoscopic biliary decompression and drainage reduces complications and mortality of patients with cholangitis due to choledocholithiasis [74]. However, it remains challenging to diagnose cholangitis in a patient with SIRS due to acute pancreatitis and its definition differs among randomized trials in pancreatitis; from Charcot's triad [75] to leaving the decision to an Expertpanel [66], or not reporting the definition of cholangitis [65,76]. Diagnostic criteria for cholangitis are not based on patients with acute (biliary) pancreatitis. Initially Charcot's triad of jaundice, abdominal pain and fever was used, later the Tokyo Guidelines (TG07) were presented to increase accuracy [77]. Recently the Tokyo Guidelines (TG13) where updated in which an inflammatory response is defined as a temperature $>38\,^{\circ}C$ or a CRP ≥ 1 mg/dL [73]. Randomized trials of ERC in biliary pancreatitis consistently used higher cut-off values implicating that the diagnosis of cholangitis in the setting of pancreatitis is a separate entity. If the TG13 are applied, it is likely that patients with acute biliary pancreatitis are misclassified with cholangitis and therefore might undergo a redundant ERC. Future research should focus on the appropriate diagnostic criteria for cholangitis in the setting of acute biliary pancreatitis.

Persistent biliary obstruction is considered as an indication for ERC [4,49,78,79], although there is no 'official' definition for biliary obstruction. Previously we mentioned the limitations of the biochemical and imaging modalities in detecting choledocholithiasis in the early setting of acute biliary pancreatitis [34]. Early ERC may be beneficial in patients with cholestasis. However, this suggestion is based on randomized trials with varying diagnostic criteria for cholestasis and enrolment of patients with or without cholestasis. A prospective observational cohort study demonstrated ERC reduced complications in patients with predicted severe pancreatitis and cholestasis [80].

There is consensus in international guidelines that ERC is not beneficial in predicted mild biliary pancreatitis [4,49,79].

International guidelines and meta-analyses are conflicting on the subject of ERC in predicted severe biliary pancreatitis [4,49,79,81]. The UK guidelines state that an urgent ERC is indicated in predicted severe biliary pancreatitis. The American Gastroenterological Association, the American College of Gastroenterology and the Italian association state that early ERC in predicted severe biliary pancreatitis without signs of cholangitis is controversial [4,49,78]. These guidelines are based on different selection, analysis and interpretation of available studies, which is explained by several limitations in the individual study designs [65,66,75,76,82]. First, different scoring systems to predict the severity of the disease and improper selection criteria were used. This increases the risk for misclassification by including patients with a predicted mild disease course and with cholangitis. In addition, no criteria were set to guarantee that the ERC was performed by an experienced endoscopist to avoid a high failure cannulation and complication rate [76,82]. The criteria for a biliary aetiology were suboptimal, so that for example in the study of Fan et al only 65% of the patients had true biliary pancreatitis. In the randomized trials the definition for 'early' ERC varied from within 24 h to 72 h after admission or onset of pain. Studies suggest that the duration of duct obstruction is correlated to the severity of the pancreatitis [62,83]. According to this, ERC should be performed as early as possible. In the studies of Neoptolemos and Fan a sphincterotomy was only performed in case CBD stones were identified at ERC [66,82]. A meta-analysis revealed that only 53% of the patients received a sphincterotomy [84], although a prospective observational study found that sphincterotomy was associated with a reduction of overall complication rate implying that sphincterotomy should be an integral part of ERC treatment [80].

A recent Cochrane meta-analysis studying the role of early ERC in gallstone pancreatitis, found no significant improvement in mortality, and local and systemic, complications, regardless of the

predicted severity [72]. Besides the limitations in study design of the included trials, the pooled sample size of patients with predicted severe biliary pancreatitis is small and thus statistically underpowered to draw definite conclusions.

The potential beneficial effect of ERC in the subgroups of predicted severe biliary pancreatitis, should be evaluated in future research with a sufficient number of patients, and statistical power, to detect differences in outcome. A randomized controlled trial in patients with predicted severe biliary pancreatitis without cholangitis is currently ongoing (ISRCTN97372133).

Key points bile duct management

- ➢ Urgent ERC is indicated in case of cholangitis.
- ➢ ERC is not indicated in predicted mild pancreatitis, regardless of persistent cholestasis.
- ➢ ERC is possibly indicated in patients with cholestasis.
- ➢ ERC is possibly indicated in patients with predicted severe pancreatitis.

Prevention of infection

Infection prophylaxis would seem a useful strategy since infectious complications have a significant impact on mortality [85]. Bacteraemia in acute pancreatitis is an independent predictor for mortality and increases the risk of infected necrosis [85].

For decades the prophylactic role of antibiotics has been subject of discussion. Randomized trials on antibiotic prophylaxis in acute pancreatitis showed conflicting results [86–89]. This is most likely caused by limitations in the study design, such as different inclusion criteria and the type of antibiotics that were used. Based on the most recent meta-analyses, guidelines advise that antibiotics should not be prescribed routinely as prophylaxis [90,91].

Selective decontamination of the intestinal tract reduces mortality in general (non-pancreatitis) intensive care unit (ICU) patients [92]. In line with these results, beneficial effects of selective decontamination in severe acute pancreatitis have been observed [93]. Although in this study, selective decontamination reduced infection of pancreatic necrosis, the study design has been criticized. The study was not placebo-controlled, nor was it blinded and no statistically significant reduction in mortality was observed. In addition, the beneficial effect might be due to the simultaneous administration of intravenous antibiotics for (suspected) non-pancreatic infections such as pneumonia. Furthermore, the potentially beneficial results should be weighed against an increase in antibiotic resistance, gram-positive overgrowth or fungi colonization [94].

Probiotic prophylaxis was hypothesized to reduce infectious complications in acute pancreatitis. A large randomized-placebo controlled trial (PROPATRIA) in patients with predicted severe pancreatitis found no effect on infectious complications but an increased rate of bowel ischaemia and mortality in patients who received probiotics [95]. Therefore, use of probiotics (at least the mixture of probiotics used in the PROPATRIA study) is strongly discouraged in patients with predicted severe pancreatitis, although the exact pathophysiological mechanism of this adverse effect remains unknown [96].

Many prophylactic strategies focus on reducing bacterial translocation in relation to the intestinal permeability [97]. Several studies have been performed to study the role of early nutrition in this respect.

Key points prevention of infection

- ➢ Intravenous antibiotics should not be used as prophylaxis.
- ➢ Enteral probiotics should not be prescribed in patient with pancreatitis.

Nutrition

Nutrition in acute pancreatitis has evolved greatly over the past decades. Initially, it was thought that feeding would stimulate pancreatic enzyme secretion and that enteral nutrition should be avoided. Over time, the key role of maintaining the integrity of the intestine became evident. Feeding became a supportive measure by which the intestinal mucosal integrity could be preserved and bacterial translocation is thought to be reduced [98,99].

Enteral nutrition has proven to be superior to parenteral nutrition regarding the occurrence of systemic infections, multi-organ failure and mortality [100]. Only in case enteral feeding is not tolerated, parenteral nutrition should be initiated to preserve adequate intake [101].

Patients with predicted mild pancreatitis can restart oral feeding on their own request. Immediate feeding has shown to be safe and leads to shorter hospital stay in patients with predicted mild pancreatitis [102]. Restrictions with regard to food consistency are not needed, i.e. a full solid diet resulted in shorter hospital stay in patients with mild pancreatitis [103].

Patients with predicted severe pancreatitis should receive nasoenteral tube feeding only if they cannot tolerate oral intake. In order to preserve the intestinal function and prevent bacterial translocation, it is recommended to initiate enteral nutrition early in the disease course [4,101]. A systematic review demonstrated that the beneficial effect of nutritional support might be associated with timing of the start of nutrition [104]. In line, a retrospective analysis of 197 cases demonstrated that early enteral nutrition (<48 h) was superior to delayed enteral nutrition (>48 h) for the prevention of infected necrosis and mortality in predicted severe acute pancreatitis [105]. A meta-analysis of early enteral feeding (<36 h of admission or within 36 h of surgery) in critically care patients showed a reduction in infectious complications and hospital stay [106]. A randomized trial in 60 patients with severe acute pancreatitis demonstrated that enteral nutrition within 48 h after admission can moderate the immune response and improve outcome compared to start of enteral nutrition after seven days [107]. A multicenter randomized trial investigating the timing of enteral nutrition in patients with predicted severe pancreatitis has recently been completed and awaits final analysis (ISRCTN18170985).

Key points nutrition

- ➢ In predicted mild pancreatitis oral intake can immediately be restarted after admission without restrictions.
- ➢ In predicted severe pancreatitis it is unclear whether early enteral nutrition improves outcome.

Recurrent biliary events

After biliary pancreatitis, cholecystectomy or endoscopic sphincterotomy should be performed in order to prevent recurrent biliary pancreatitis, biliary colics and cholecystitis [4,79]. Endoscopic sphincterotomy has shown to reduce the risk of recurrent biliary pancreatitis, but not of other biliary events, such as cholecystitis or biliary colics [108]. Therefore, one should strive to always perform a cholecystectomy early following an attack of biliary pancreatitis unless this is not safe or feasible, e.g. in older or unfit candidates or in patients with extrapancreatic collections. In these cases endoscopic sphincterotomy is acceptable [109]. Although sphincterotomy clearly will not prevent recurrent biliary colics it will virtually eliminate the risk of recurrent biliary pancreatitis [108,110].

The timing of cholecystectomy after mild biliary pancreatitis still is subject to debate. As recurrent events occur particularly in the first months after recovery from pancreatitis, one should aim for quick definitive management, provided that cholecystectomy can be performed safely [108,110]. Delay of cholecystectomy increases the risk of a recurrent biliary event. A randomized trial investigating the timing of cholecystectomy was prematurely stopped because a beneficial effect in favour of cholecystectomy within 48 h after admission was observed [111]. These results should be interpreted with some caution as the study was not adequately powered to study safety. A recent systematic review

found a readmission rate prior to cholecystectomy in 95 of 515 patients (18%) because of recurrent biliary pancreatitis, acute cholecystitis, and biliary colics after mild biliary pancreatitis. This study further showed that early cholecystectomy is probably safe after mild biliary pancreatitis although selection bias could not be fully excluded [110]. Currently a randomized trial is investigating the efficacy and safety of index cholecystectomy after biliary pancreatitis (ISRCTN72764151) [112].

In severe pancreatitis, with local and systemic complications, cholecystectomy is delayed until resolution of symptoms or when extraperancreatic collections are resolved, which is usually after six weeks [79,113]. Little is known about the recurrent events after severe pancreatitis prior to cholecystectomy and of the role of endoscopic sphincterotomy. In two retrospective studies no recurrent events were reported [113,114].

Key points recurrent biliary events

- ➢ Cholecystectomy should be performed after biliary pancreatitis to reduce the risk of recurrent biliary events.
- ➢ In mild pancreatitis current evidence is that cholecystectomy should be performed as soon as possible after recovery. A randomized trial is needed.
- ➢ In severe pancreatitis cholecystectomy should be delayed until resolution of symptoms or when extraperancreatic collections are resolved.

Intensive care

The intensity of clinical monitoring in acute pancreatitis is best based on the presumed risk of deterioration and therefore the predicted severity of acute pancreatitis. Clinical parameters, described by the Society of Critical Care Medicine, can be used to triage for ICU admission [115]. The crux in the management with acute pancreatitis is adequate fluid resuscitation (see section fluid therapy) and to be aware of the occurrence of early complications that require intervention. Rapid deterioration might be due to an abdominal compartment syndrome (ACS). A 2013 international conference of experts defined ACS as an intra-adominal pressure of $>$20 mmHg and new organ failure [116]. Sometimes a period of intra-abdominal hypertension (IAH), defined as $\geq$12 mmHg, is observed prior to the new onset of organ failure. ACS and IAH have shown to contribute in gut barrier failure [117]. Reported incidence rates of IAH are high between 59 and 78% in acute pancreatitis and a portion of 27% developed ACS [118,119]. An extremely high mortality rate of ACS up to 83% has been described [120].

The initial step in the treatment of ACS is to immediately lower abdominal pressure using nasogastric decompression, laxantia and muscle relaxants [116]. If clinical improvement is not achieved, percutaneous drainage of intra-peritoneal fluid should be attempted. If this does not suffice, surgical decompressive laparotomy is probably indicated. Animal studies suggest that there is a narrow time window for surgical intervention [121–123]. A randomized trial comparing decompressive laparotomy with percutaneus puncture with placement of abdominal catheter in patients with severe pancreatitis and ACS, is currently ongoing (NCT00793715) [124].

Key point intensive care

- ➢ Abdominal compartment syndrome is associated with high mortality and requires prompt intervention.
- ➢ Optimal treatment of abdominal compartment syndrome is currently unclear.
- ➢ There is a 2013 international consensus guideline on the management of abdominal compartment syndrome [116].

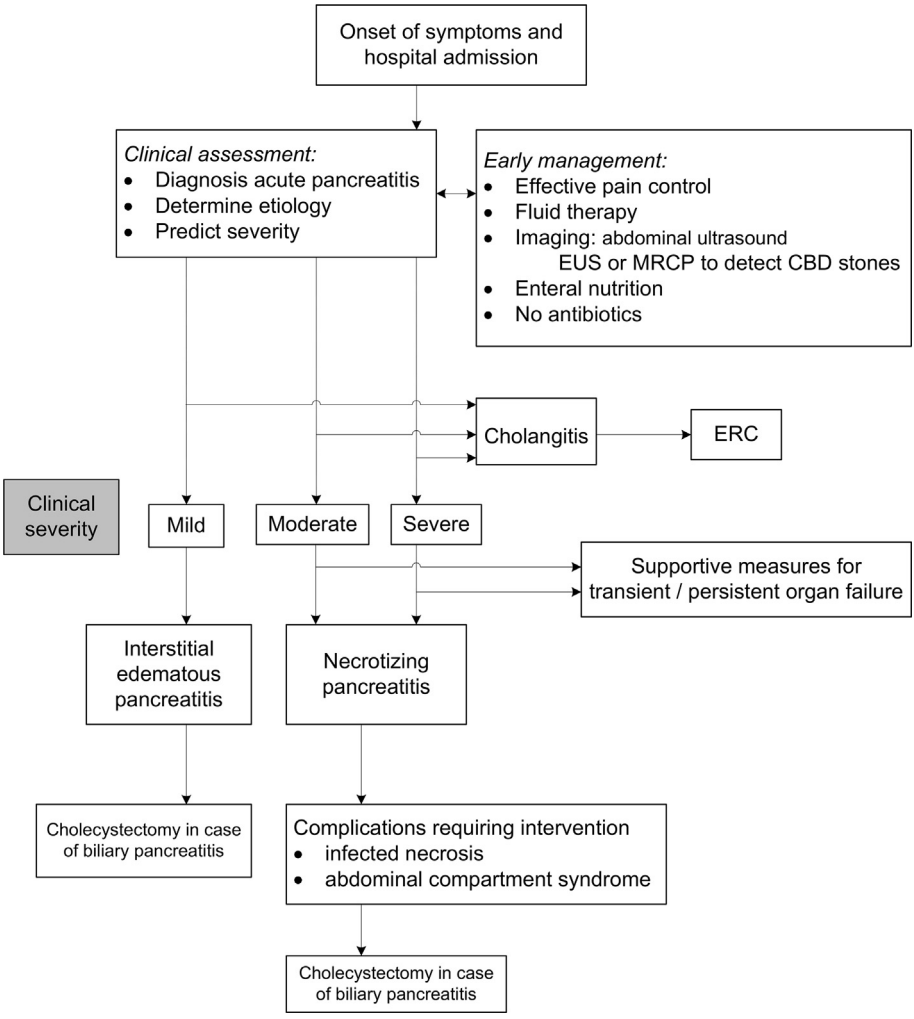

Fig. 1. Flow-chart early management of acute pancreatitis.

Necrotizing pancreatitis

Sterile necrosis can be treated without invasive intervention in the vast majority of patients [18]. Around 30% of patients will develop infected necrosis [5,6]. Infected necrosis increases the death rate to approximately 30% [15,18]. Infection is considered proven if gas is present in the extrapancreatic collection or when fine-needle aspiration is positive for bacteria or fungi on gram stain and culture [6,125]. There is no need for routine fine-needle aspiration in patients with clear clinical or imaging signs of infected necrotizing pancreatitis as there is a small (10–25%) risk of false negative results [126,127]. It is generally accepted to administer intravenous antibiotics in case of suspected infected necrosis to mitigate additional infectious complications [128]. Intervention to drain infected fluid or remove infected necrosis is justified in patients with progressive clinical deterioration despite maximal supportive therapy [18]. Currently it is common practice that intervention should be delayed until approximately four weeks in order to minimize the risks of complications during intervention, in particular necrosectomy [18].

Infected necrosis should be treated by a step-up approach [18,129], consisting of catheter drainage, either percutaneously or endoscopic transluminal, if necessary followed by surgical or endoscopic

necrosectomy. A pilot randomized trial found endoscopic transgastric necrosectomy to be superior to surgical necrosectomy in terms of new organ failure and overall complications [130]. An adequately powered randomized trial, comparing the surgical step-up approach versus the endoscopic step-up approach in patients with infected pancreatic necrosis, is currently ongoing (ISRCTN09186711).

Key points necrotizing pancreatitis

- ➢ Infected necrosis is nearly always an indication for intervention.
- ➢ Interventions should ideally be postponed until the collection has become walled-off (typically >4 weeks) as this reduces complications.
- ➢ Infected necrosis should be treated by a step-up approach, which starts with catheter drainage, if needed followed by (minimally invasive) necrosectomy.

Summary

Acute pancreatitis is a common disease with a rising incidence. Recently, the revised Atlanta classification presented new definitions on clinical severity and new terminology for extrapancreatic collections (Table 1). Diagnosing acute pancreatitis also involves predicting the severity and establishing the aetiology to tailor management strategies in the early phase of acute pancreatitis. Recent guidelines recommend SIRS as marker to predict severity because of its ease of use and its ability to perform as good as complex models. An elevated ALAT (>150 IU/L) indicates a high probability of a biliary origin. MRCP or EUS should be performed to detect the presence or absence of CBD stones.

Early management strategies in pancreatitis are based on preventing or treating organ failure and preventing infectious complications (Fig. 1). Fluid resuscitation at an infusion rate of 5–10 ml/kg/h is regarded as a cornerstone in the treatment of pancreatitis, although high quality studies supporting its use are eagerly awaited. The approach to nutrition and feeding in acute pancreatitis has radically changed over time. A pro-active approach with early enteral feeding is advocated in order to maintain gut integrity. In mild pancreatitis oral intake can usually be resumed quickly after hospital admission. In severe pancreatitis it is unclear whether early enteral nutrition improves outcome. Antibiotics should not be administered prophylactic. In case of biliary pancreatitis, urgent ERC should be performed only in case of cholangitis and possibly in patients with cholestasis. ERC is not indicated in predicted mild pancreatitis. In predicted severe biliary pancreatitis, the role of early ERC still needs to be determined. Cholecystectomy should be performed early to reduce readmissions for biliary events. In cases with severe pancreatitis it is appropriate to delay cholecystectomy to six weeks after the onset of acute pancreatitis. In patients with severe acute pancreatitis, rapid deterioration may be due to abdominal compartment syndrome or infected pancreatic necrosis which are conditions that are associated with a high mortality rate and require intervention.

Practice points

- Acute pancreatitis is the most common gastro-intestinal reason for acute hospitalization and the incidence is rising.
- An elevated ALAT >150 IU/L (2.55 μkat/L) is a good predictor for a biliary origin.
- Initial treatment should consist of:
  - Effective pain control
  - Infusion rate 5–10 ml/kg/h, adjusted upon clinical response
  - Imaging: abdominal ultrasound at admission. EUS or MRCP to detect CBD stones.
- ERC does not improve outcome in predicted mild biliary pancreatitis.
- Urgent ERC with sphincterotomy is indicated in case of cholangitis.
- Extrapancreatic fluid collections are classified as acute extrapancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis.

Research agenda

- Accurate markers to predict severity of the disease course.
- Validation of the proposed classifications for severity of pancreatitis.
- Fluid therapy in acute pancreatitis.
- Diagnostic criteria for cholangitis in the setting of acute biliary pancreatitis.
- Role of early ERC in predicted severe biliary pancreatitis.
- Timing of enteral nutrition in predicted severe pancreatitis.
- Timing of initial intervention in infected necrotizing pancreatitis.

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Conflict of interest

None.

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