

Acute pancreatitis: recent advances through randomised trials

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ABSTRACT

Acute pancreatitis is one of the most common GI conditions requiring acute hospitalisation and has a rising incidence. In recent years, important insights on the management of acute pancreatitis have been obtained through numerous randomised controlled trials. Based on this evidence, the treatment of acute pancreatitis has gradually developed towards a tailored, multidisciplinary effort, with distinctive roles for gastroenterologists, radiologists and surgeons. This review summarises how to diagnose, classify and manage patients with acute pancreatitis, emphasising the evidence obtained through randomised controlled trials.

BACKGROUND

With over 26 000 hospital admissions in the UK each year, acute pancreatitis is among the most common GI conditions requiring acute hospitalisation.¹ The worldwide incidence of acute pancreatitis is rising, thus further increasing its burden on healthcare services.² Acute pancreatitis is an inflammatory process which causes a local and systemic inflammatory response syndrome (SIRS). Although the majority of patients have a mild disease course, around 20% will develop moderate or severe pancreatitis, with necrosis of the (peri)pancreatic tissue and/or (multiple-)organ failure (figure 1).³

Over the last decades, the treatment of acute pancreatitis has gradually developed towards a tailored, multidisciplinary approach, with a distinctive role for endoscopic, radiological and surgical treatment strategies. Much of the new evidence on the treatment of acute pancreatitis arises from randomised controlled trials (RCTs), which are universally considered as the reference standard for comparing treatment strategies in medicine. Random allocation of patients, if possible blinded, keeps all known and unknown variables constant except for the allocated treatment, thereby measuring the ‘true’ effect of the investigated treatment. In the past decade, numerous RCTs have had a great impact on the treatment of acute pancreatitis. This review provides an overview of current clinical practice concerning the diagnosis, classification and treatment of acute pancreatitis, while focussing on the outcomes of these RCTs.

METHODS

For this review, the most recent international evidenced-based guidelines on acute pancreatitis, the 2012 International Association of

Significance of this study

Early phase

- ▶ Primary management of acute pancreatitis consists of (early goal-directed) fluid resuscitation with Ringer’s lactate and adequate pain control.
- ▶ Endoscopic retrograde cholangiography/ endoscopic sphincterotomy should be performed urgently in case of concomitant cholangitis, should not be performed in predicted mild biliary pancreatitis and is controversial in predicted severe biliary pancreatitis.
- ▶ Prophylactic use of antibiotics or probiotics is not indicated.
- ▶ In patients with acute pancreatitis, regardless of severity, a normal oral diet can be started once the acute pain is resolving.
- ▶ Nasoenteric tube feeding is indicated only when sufficient oral intake is not reached after 3–5 days.

Beyond the early phase

- ▶ Cholecystectomy should be performed during the index admission for mild biliary pancreatitis.
- ▶ Intervention for infected necrotising pancreatitis should preferably be delayed until the phase of walled-off necrosis.
- ▶ The step-up approach, either endoscopic or surgical, is the preferred treatment of infected necrotising pancreatitis.

Aftercare

- ▶ In (presumed) idiopathic pancreatitis, a repeat abdominal ultrasound and ultimately endoscopic ultrasound may detect microlithiasis/sludge in up to half of patients, warranting cholecystectomy.
- ▶ Alcohol abstinence support programmes can prevent recurrent alcoholic pancreatitis.
- ▶ Attention should be paid to potential endocrine and exocrine insufficiency after necrotising pancreatitis.

Pancreatology/American Pancreatic Association (IAP/APA) guidelines,⁴ were used as the starting point. PubMed was searched for studies, specifically RCTs, published after the IAP/APA guideline using the following terms: Pancreatitis (MeSH Terms) OR

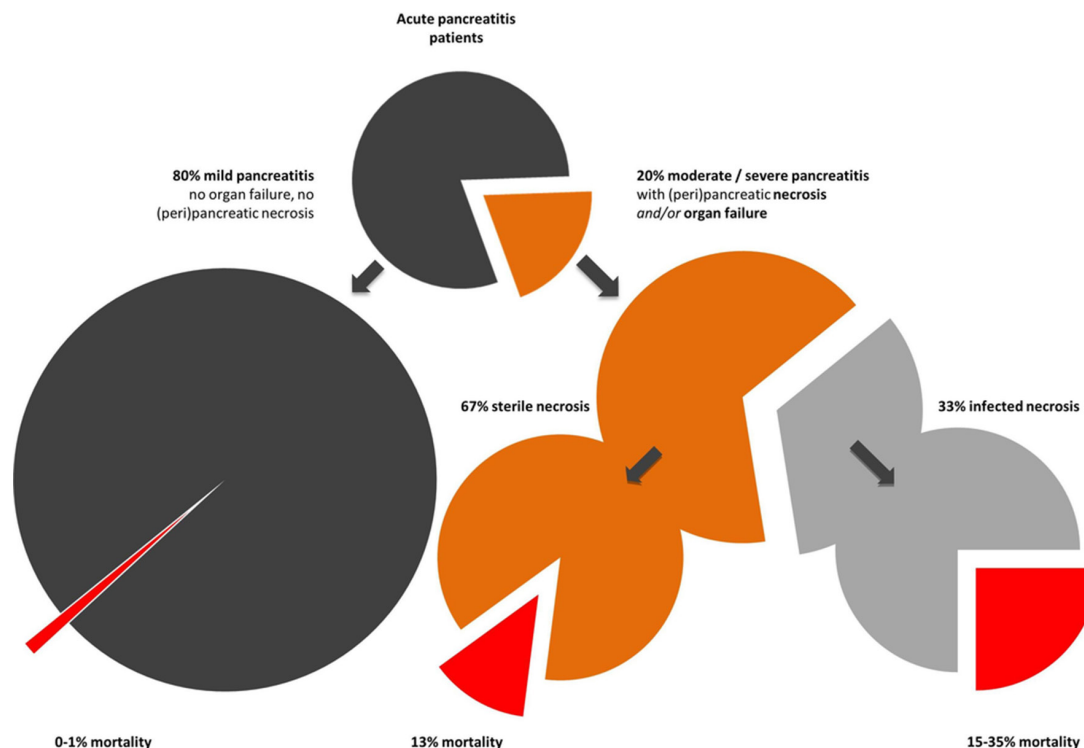


Figure 1 Mortality rates of acute pancreatitis.

(acute pancreatitis (Title)). All articles regarding chronic pancreatitis and malignant disease were excluded. Two authors (SvD and NH) assessed all English articles concerning RCTs on adults published between June 2012 and February 2017. In total, 490 articles were found, of which all potential 'practice changing' RCTs were incorporated within this review. Additionally, relevant articles from the reference list of the included articles were reviewed as well as new, evidence-based guidelines on acute pancreatitis published after the IAP/APA guideline.

EARLY PHASE OF ACUTE PANCREATITIS

Diagnosis

According to the 2012 Revised Atlanta Classification, the diagnosis acute pancreatitis requires 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 the normal value or (3) findings consistent with acute pancreatitis on imaging (contrast-enhanced CT (CECT), MRI or ultrasound).⁵ In case of typical clinical and laboratory findings, an additional CECT or other cross-sectional imaging is not required to confirm the diagnosis. The severity of acute pancreatitis is classified as mild, moderate or severe. Mild when there are no local or systemic complications present; moderate in case of local (eg, peripancreatic fluid collections) or systemic complications (eg, exacerbation of chronic disease) or transient organ failure (<48 hours) and severe in case of persistent organ failure (>48 hours).⁵

Aetiology

In Western countries, gallstones and/or biliary sludge are the most prevalent (approximately 40%–50%) cause of acute pancreatitis.^{6,7} With approximately 20% of cases, alcohol is the second most frequent cause of acute pancreatitis in most countries.⁶⁻⁸ Less frequent causes of acute pancreatitis include

medication, endoscopic retrograde cholangiopancreatography, hypercalcaemia, hypertriglyceridemia, surgery and trauma.

Determining the aetiology of acute pancreatitis is of importance, as it partly drives early management as well as the follow-up strategy. Standard work-up of acute pancreatitis includes medical history, physical examination, laboratory tests (liver enzymes, triglycerides, calcium) and transabdominal ultrasound. In 10%–25% of cases, the aetiology of the pancreatitis remains unclear. Idiopathic pancreatitis requires additional diagnostic work-up in the form of a repeat transabdominal ultrasound and ultimately an endoscopic ultrasound (EUS).⁴ Meta-analyses show that in around 61% of cases, an aetiology can be established by EUS. This includes the detection of microlithiasis or biliary sludge (41%), for which cholecystectomy is

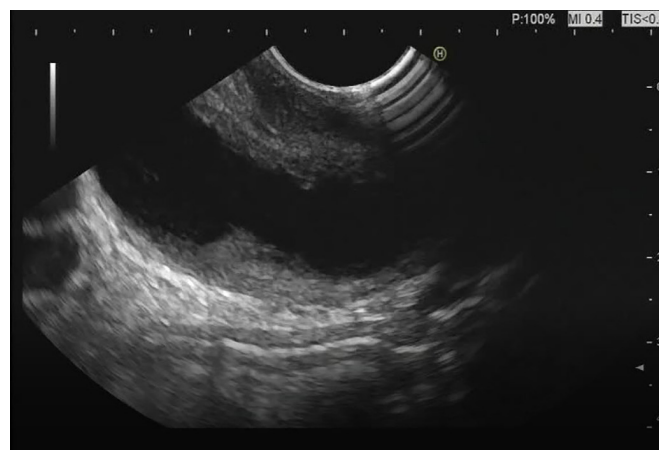


Figure 2 Linear endoscopic ultrasound image of sludge in the gallbladder.

required to prevent recurrences (figure 2), but also other causes such as chronic pancreatitis or pancreatic tumours.⁹

Prediction of severity

Prediction of severity of acute pancreatitis is used to identify patients at low or high risk of developing complications. This is useful both for triaging patients for the proper level of monitoring and for stratification of patients for inclusion in RCTs. Multiple scoring systems are available that combine clinical and laboratory findings to determine the likelihood of a severe disease course: the Acute Physiology and Chronic Health Evaluation II (APACHE-II), Ranson score, modified Glasgow/Imrie score, SIRS criteria, Bedside Index for the Severity in Acute Pancreatitis and Harmless Acute Pancreatitis Score, while single laboratory parameters such as C reactive protein (CRP) can also be used.

Approximately 50% of all patients have predicted severe pancreatitis. Although only half of these will ultimately develop (moderately) severe pancreatitis, virtually none of the patients with predicted mild pancreatitis will do so. Mortality of predicted severe pancreatitis is approximately 10%, as compared with <1% in patients with predicted mild pancreatitis. The scoring systems are therefore primarily used to exclude the possibility of developing severe pancreatitis. Since the accuracy of the various predictive scoring systems is comparable,¹⁰ the IAP/APA guideline advises to use persistent (>48 hours) SIRS because of its relative simplicity.⁴

Treatment in the acute phase

As no curative therapy is currently available for acute pancreatitis, early treatment consists of supportive care which includes adequate fluid resuscitation and pain management.

Fluid resuscitation

Inflammation of the pancreas and the accompanying systemic inflammatory response leads to extravasation of fluid to the third space. In severe cases this may cause hypovolaemia, hypoperfusion and ultimately organ failure. To counteract this cascade, adequate fluid resuscitation is needed. Few RCTs studied the type of fluids. In critically ill patients in general, colloids are discouraged since there is no evidence to support their effectiveness whereas hydroxyethyl starch might even increase mortality.¹¹ The IAP/APA guideline therefore proposes crystalloids in the form of Ringer's lactate. This is based on one multi-centre RCT in 40 patients with acute pancreatitis that showed beneficial effects on CRP levels and SIRS with Ringer's lactate as compared with normal saline.^{4,12} This advantage of Ringer's lactate or other balanced fluids (eg, Plasma-Lyte) over normal saline in pancreatitis patients has however not been confirmed by larger RCTs. Further studies are needed as multiple RCTs in the general intensive care setting have so far failed to find better outcomes when using balanced fluids.^{13–16}

Five RCTs using different fluid resuscitation protocols have been conducted.^{12,17–20} Two of these RCTs in 76 and 115 patients with severe acute pancreatitis show that rapid, uncontrolled fluid resuscitation (10–15 mL/kg/h or until a haematocrit <35% within 48 hours) significantly worsened the rates of infections, abdominal compartment syndrome, the need for mechanical ventilation and even mortality.^{17,18}

One RCT in 60 patients with predicted mild pancreatitis demonstrated that aggressive fluid hydration with Ringer's lactate (20 mL/kg bolus followed by 3 mL/kg/h) compared with standard hydration with Ringer's lactate (10 mL/kg bolus

followed by 1.5 mL/kg/h) improved a composite end point (ie, 'clinical improvement within 36 hours').¹⁹ So, both too little as well as too much fluid administration in the acute phase of pancreatitis can be harmful, possibly dependent on the severity of the pancreatitis. As advised by the IAP/APA guideline, early goal-directed therapy with adequate monitoring might therefore remain the preferred solution.⁴

Early goal-directed therapy was the subject of one multi-centre RCT in 40 acute pancreatitis patients and one RCT in 200 patients with severe acute pancreatitis.^{12,20} The first RCT could not confirm superiority of early goal-directed therapy, but the incidence of SIRS in the entire RCT was very low, suggesting less severe pancreatitis patients. The second RCT showed reductions in the duration of mechanical ventilation and in the rates of multiple organ failure and mortality in the early goal-directed therapy group, especially if fresh frozen plasma was added as a resuscitation fluid. However, as baseline APACHE-II scores were significantly worse in the control group, suggesting non-balanced randomisation, further RCTs are needed.

It is difficult to draw conclusions based on these RCTs as multiple of the three main parameters of interest (fluid type, fluid protocol and resuscitation goals) differ between trials. Since no single parameter adequately reflects hydration status, it is therefore advised to observe trends in multiple parameters. On the nursing ward, target measures include a heart rate <120/min, a mean arterial pressure between 64 and 85 mm Hg and a urinary output of at least 0.5 mL/kg/h. Relevant laboratory findings include blood urea nitrogen, creatinine levels and especially haematocrit, which should stay between 35% and 44%.⁴

Pain management

Pain is the predominant symptom of acute pancreatitis and should be treated promptly and adequately. Frequent reassessment of pain scores and, if indicated, adjustment of analgesic types and/or dosages is needed to assure proper pain management. Several RCTs compared different types of analgesia in acute pancreatitis.^{21–28} A systematic review on opioid use in acute pancreatitis and a recent meta-analysis reported that the quality of the majority of these RCTs is low and no particular analgesic strategy is superior.^{29,30} As current evidence is limited, pain can be managed according to general state-of-the-art pain protocols.

Antibiotics and probiotics as prophylaxis

One of the most lethal complications of acute pancreatitis is secondary infection of pancreatic or peripancreatic necrosis.³¹ This is thought to occur as a result of bacterial translocation from the gut.³² Several double-blind RCTs failed to show a reduction of infection of (peri)pancreatic necrosis through the prophylactic use of antibiotics,^{33–35} as confirmed by meta-analyses.^{36,37} Antibiotics are therefore only indicated when infection is either proven or clinically suspected. In order to prevent bacterial translocation, attempts were made to influence the intestinal microbiome using probiotic bacteria. Two RCTs compared probiotic bacteria with placebo in 62 and 45 patients with severe acute pancreatitis and reported promising results.^{38,39} A subsequent multicentre RCT* in 296 patients with predicted severe pancreatitis, however, showed increased rates of mortality and non-occlusive mesenteric ischaemia in patients receiving probiotics.⁴⁰ Therefore, administration of probiotics is currently considered contraindicated in the treatment of (predicted) severe pancreatitis.

Nutrition

Enteral nutrition does not only provide adequate caloric intake, it may also improve clinical outcomes. It has been hypothesised that the combination of disturbed intestinal motility, bacterial overgrowth and increased permeability of the gut can lead to bacterial translocation, thus causing infection of pancreatic necrosis.^{32 41–45} Enteral nutrition may reduce translocation by stimulating intestinal motility, reducing bacterial overgrowth and thereby maintaining mucosal gut integrity.^{46 47} A Cochrane review involving eight RCTs confirmed this, showing reduced rates of infection, organ failure and mortality in 348 patients with acute pancreatitis receiving routine enteral nutrition as compared with routine total parenteral nutrition.⁴⁸

Furthermore, the timing of initiation of enteral nutrition could also be relevant. Some retrospective studies suggested that an early start of nasoenteric feeding significantly reduced infection rates.^{49–51} A multicentre RCT* in 208 patients with predicted severe pancreatitis, comparing very early nasojejunal feeding (<24 hours) with introduction of an oral diet after 72 hours (with on-demand nasojejunal feeding) showed no beneficial effects on infection rates or mortality. Importantly, in the control group, 69% of patients did not require a nasoenteral tube, thus avoiding potential patient discomfort.⁵² A second recent RCT, comparing early nasojejunal feeding (<24 hour) with no nutritional support in 214 patients, also failed to show benefits from early nutritional support.⁵³ Based on these RCTs, tube feeding in predicted severe pancreatitis can be limited to those patients who have insufficient oral caloric intake after 3–5 days.

It was previously believed that nasogastric feeding in acute pancreatitis would increase the risk of aspiration, and increase inflammation and pain as a result of stimulation of the pancreatic excretion. However, three RCTs found nasogastric feeding non-inferior to nasojejunal feeding.^{54–56} Consequently, both routes of enteral feeding are now considered feasible and safe.⁵⁷ In patients with (predicted) mild pancreatitis, three RCTs have shown that a normal oral diet can be resumed once the pain is decreasing.^{58–60}

Endoscopic retrograde cholangiography in biliary pancreatitis

In patients with acute biliary pancreatitis, (transient) obstruction at the level of Vater's ampulla is thought to initiate pancreatic inflammation. Persisting biliary obstruction may aggravate the disease course. Early biliary decompression and stone removal using endoscopic retrograde cholangiography (ERC) with endoscopic sphincterotomy (ES) has therefore been extensively studied as a potential intervention to improve clinical outcomes in biliary pancreatitis. Common bile duct (CBD) stones may, however, pass into the duodenum spontaneously, in which case ERC with ES might be redundant and even harmful. Several RCTs have shown that early ERC is not effective in patients with predicted mild pancreatitis,^{61–63} as the potential benefits do not outweigh the procedural risks.

Emergency ERC with ES is indicated within 24 hours after diagnosing acute biliary pancreatitis with concomitant cholangitis.^{4 64} Importantly, diagnosing cholangitis in patients also suffering from SIRS, as is commonly seen in the early phase of (predicted severe) biliary pancreatitis, can be challenging. The definition of cholangitis differs between trials and includes Charcot's triad,⁶¹ expert opinion⁶⁵ and the updated Tokyo guidelines (TG13) for acute cholangitis.⁶⁶ These definitions do not take into account the underlying cause, namely acute pancreatitis, and have low thresholds regarding the presence of inflammation and cholestasis. This may lead to overdiagnosing of acute

cholangitis in acute pancreatitis, potentially exposing patients to unnecessary ERC procedures.⁶⁶ Further research is needed to establish appropriate diagnostic criteria for cholangitis in acute biliary pancreatitis patients.

The use of routine (early) ERC with ES in predicted severe biliary disease course is controversial. Several RCTs,^{61–63 65 67 68} subsequent meta-analyses and guidelines provide conflicting advice on this issue.⁶⁹ A possible explanation for these discrepancies are the differences in the definitions used for biliary pancreatitis and cholangitis, as well as differences in patient populations and in timing and quality of the ERC. For example, in some studies, ERC was performed in non-biliary pancreatitis; in other studies, patients with cholangitis were randomised while these patients should always undergo ERC and sphincterotomy was not performed routinely. Recently, a multicentre RCT* comparing routine early ERC plus ES with conservative treatment in 232 patients with predicted severe acute biliary pancreatitis but without cholangitis was completed and results are awaited (the APEC-trial, ISRCTN97372133).⁷⁰

The use of EUS for the detection of CBD stones is emerging in biliary pancreatitis. The sensitivity and specificity of EUS for CBD stone detection are superior to both transabdominal ultrasound and serum markers. As ERC with ES is presumably most effective in patients with persisting CBD stones, an EUS-first strategy to establish the indication for ERC with ES in acute biliary pancreatitis patients could improve outcomes. A meta-analysis comparing an EUS-first strategy with ERC including one RCT in 140 patients showed promising results. Around 71% of ERC procedures could be avoided without a negative effect on the clinical course of the pancreatitis.^{71 72} A recent prospective cohort study supports these observations.⁷³ Furthermore, a decision tree analysis on cost-effectiveness demonstrated that, especially in patients with severe acute biliary pancreatitis, an EUS-first method is less costly than ERC only.⁷⁴ Further research is needed to confirm the effectiveness and feasibility of this relatively new strategy.

BEYOND THE EARLY PHASE

Imaging

The 1992 Atlanta Classification was a global consensus on how to define acute pancreatitis and how to classify the severity and local pancreatic complications.³¹ In 2012, the Atlanta classification was revised to better define the morphology of acute pancreatitis and (peri)pancreatic collections as seen on CECT.⁵ The revised Atlanta classification distinguishes interstitial oedematous pancreatitis from necrotising pancreatitis, wherein the latter is subdivided in parenchymal and peripancreatic necrosis (figure 3). In most cases, a combination of parenchymal and peripancreatic necrosis is seen.⁵ In the first 3–4 days of acute pancreatitis, CECT is unreliable for determining the extent of necrosis and the presence of collections.^{75 76} Only patients suspected of having abdominal catastrophes, such as perforation, bleeding or ischaemia, should have an urgent CECT.^{76 77} If patients fail to improve after 5–7 days of initial treatment, a CECT can determine the presence and extent of necrosis and (peri)pancreatic collections.^{4 64}

The terminology of (peri)pancreatic collections has changed in the revised Atlanta classification.⁵ In case of interstitial pancreatitis, these collections are referred to as 'acute pancreatic fluid collections', and in case of necrotising pancreatitis as 'acute necrotic collections' (ANC). Over time, acute collections either resolve spontaneously or mature with encapsulation of fluid and/or necrotic tissue. In ANC, this leads to walled-off necrosis

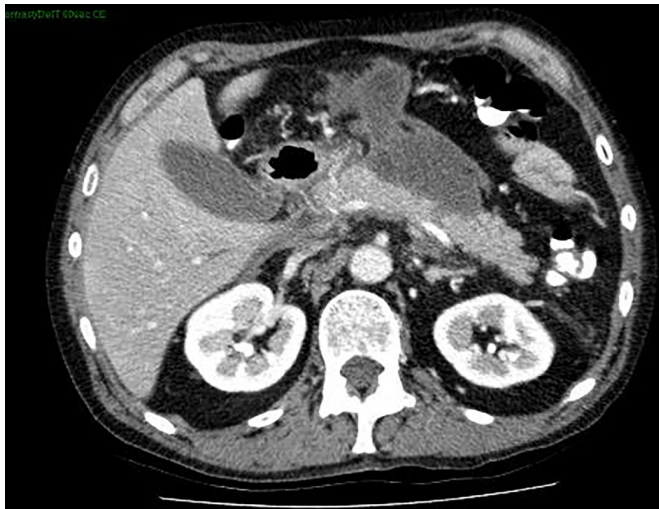


Figure 3 Peripancreatic necrosis—a form of necrotising pancreatitis.

(WON) (figure 4).^{5 78} The process of encapsulation mostly takes around 4–6 weeks. If the necrotic collections remain sterile, patients can be treated conservatively. Intervention is only indicated in case of infection. In sterile collections, interventions should only be considered in case of mechanical obstruction and/or failure to thrive which persists for 6–8 weeks.

INFECTED NECROTISING PANCREATITIS

Collections with necrosis (ie, ANC, WON) become infected in about one-third of patients.⁷⁹ Infected necrotising pancreatitis has a mortality of 15%.³ Infection can be diagnosed in three ways: (1) by gas configurations in the necrotic collection on imaging (figure 5),⁵ (2) by a positive gram stain or culture from a (percutaneous) fine-needle aspiration of the necrotic collection⁸⁰ or (3) suspected by clinical diagnosis. Clinical suspicion of infection is based on signs of infection (temperature $>38.5^{\circ}\text{C}$, rising serum inflammatory markers) or when new/persistent organ failure occurs, which is typically most reliable after the initial phase of SIRS.^{4 81 82}

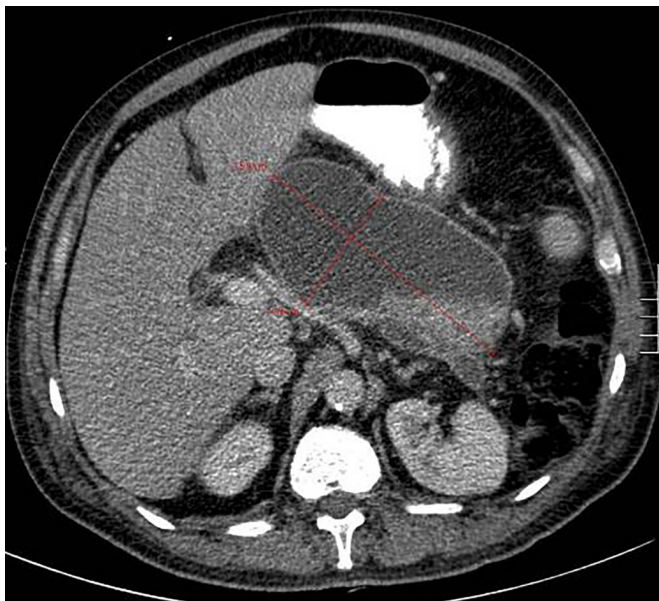


Figure 4 Walled-off necrosis—a form of necrotising pancreatitis.

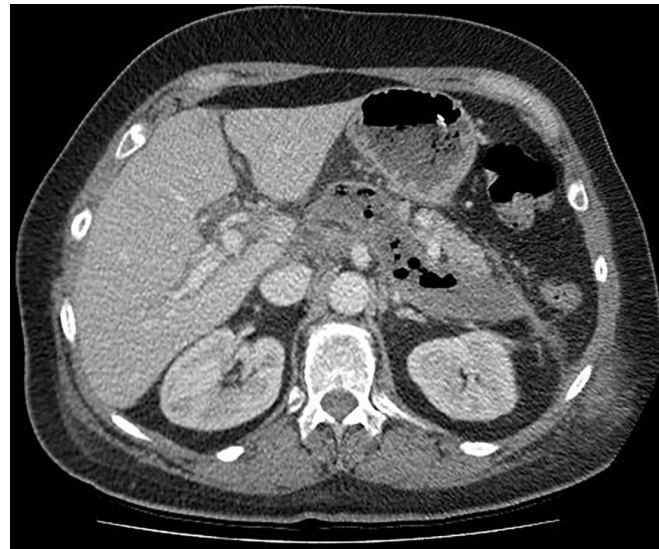


Figure 5 Infected necrotic collection, with gas configurations, on day 20 after onset of disease. Not fully encapsulated.

If infection of a necrotic collection is proven or clinically highly suspected, antibiotic treatment is indicated. The preferred antibiotics are broad-spectrum, with the capability of penetrating the necrotic pancreatic tissue, according to local antibiotics protocol. A positive culture may be used to switch to targeted antibiotics. Although there are some series with high success rates of solely antibiotic treatment, most patients will eventually need an intervention (ie, catheter drainage, necrosectomy) to treat infected necrosis (figure 6).^{82–84} Antibiotics are therefore mostly used to support patients until collections become encapsulated (WON). This is presumed to facilitate safer interventions with a lower risk of bleeding and less reinterventions. Some experts, however, question this delay in treatment and suggest immediate catheter drainage.⁸⁵ A multicentre RCT* is currently comparing immediate versus postponed drainage in 104 patients with infected necrotising pancreatitis (POINTER trial; ISCRTN33682933).

Intervention

Historically, patients with necrotising pancreatitis underwent early laparotomy to debride the necrotic tissue. This was associated with high mortality rates, probably because these often severely ill patients could not endure the extra ‘hit’ of the surgical trauma.^{86 87} Current guidelines therefore advocate to delay interventions until the stage of WON.^{4 64} In a multicentre RCT*, 88 patients with infected necrotising pancreatitis were randomised between necrosectomy via laparotomy or a step-up approach. This approach consisted of percutaneous catheter drainage followed, in case of lack of clinical improvement, by video-assisted retroperitoneal debridement.⁸² The step-up approach reduced the composite end point (ie, death or major complications) from 69% to 40% (risk ratio (RR) 0.57; 95% CI 0.38 to 0.87; $p=0.006$). Another finding was that 35% of patients in the step-up arm could be treated with catheter drainage only, and did not require a necrosectomy.⁸²

The step-up approach is now considered the standard practice of care for patients with infected pancreatic necrosis and has been implemented in all major guidelines.^{4 64} Catheter drainage is only followed by necrosectomy when clinically indicated. Several methods of surgical necrosectomy are available, either open or minimally invasive techniques. As RCTs comparing these methods ‘head-to-head’ are lacking, the optimal method of necrosectomy

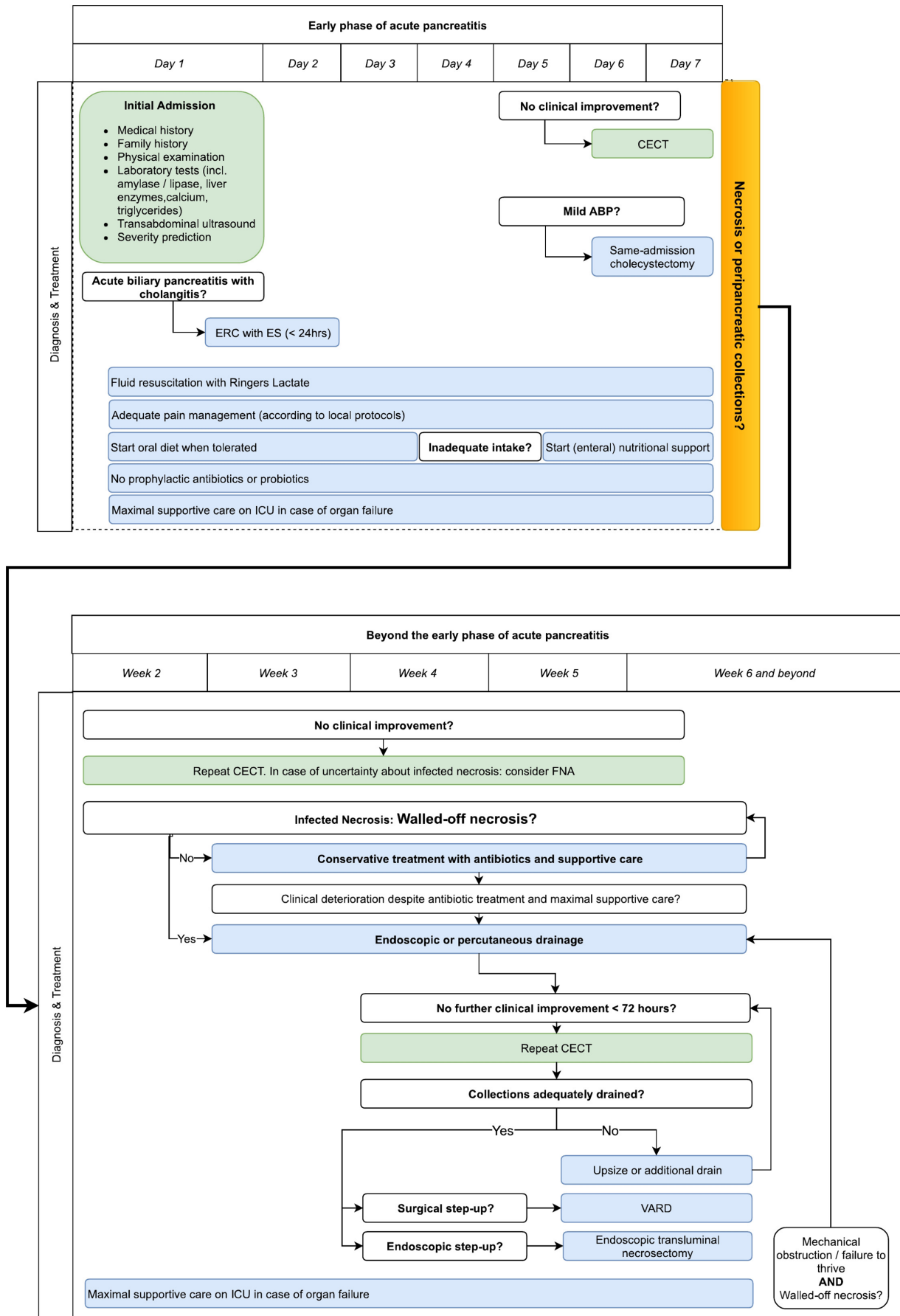


Figure 6 Flowchart acute pancreatitis. CECT, contrast-enhanced CT; ERC, endoscopic retrograde cholangiography; ES, endoscopic sphincterotomy; VARD, video-assisted retroperitoneal debridement.

remains unclear. Retrospective studies suggest a decreased risk of complications using minimally invasive techniques.^{88 89}

The step-up approach can also be performed endoscopically. In 2000, endosonography-guided transgastric necrosectomy was first described. It avoids general anaesthesia and may further reduce the surgical stress and complications.⁹⁰ The technique has since been reported in several retrospective cohort studies.^{91 92} A multicentre pilot RCT* in 20 patients found a reduction in the primary end point of proinflammatory response and in the combined secondary end point of major complications in patients undergoing endoscopic necrosectomy, compared with minimal invasive surgical necrosectomy.⁹³ Although promising, this was a pilot RCT and did not include a step-up approach. A subsequent multicentre RCT*, including 98 patients, comparing an endoscopic step-up approach with a surgical step-up approach has recently been completed and results are awaited (TENSION trial, ISRCTN09186711).⁸¹

AFTERCARE

Prevention of recurrence

Some 17%–22% of patients will have a recurrent pancreatitis and 8%–16% of patients will develop chronic pancreatitis.^{94–96} Several studies have attempted to reduce recurrence rates, most of them addressing the underlying cause of the disease. In patients with alcoholic pancreatitis, supervised alcohol abstinence should be advised, as continuation of alcohol consumption increases the risk of recurrence and ultimately of chronic pancreatitis.^{97–99} Smoking is an additional, but poorly recognised, risk factor for recurrent acute and chronic pancreatitis.⁹⁴ One RCT in 120 patients showed that repeated outpatient clinic visits with an intervention against alcohol consumption reduces the recurrence of pancreatitis, compared with a single intervention.¹⁰⁰ However, adherence to these abstinence programmes remains poor.¹⁰¹

In patients with biliary pancreatitis, cholecystectomy will reduce the risk of recurrence but its optimal timing has been debated. In severe biliary pancreatitis, it is common practice to delay cholecystectomy until the patient has recovered and local signs of inflammation have resolved or until at least 6 weeks after discharge.¹⁰² In mild biliary pancreatitis, current guidelines recommend cholecystectomy during the same hospital admission. Several clinical audits have shown that guideline adherence is poor, cholecystectomy is often delayed.^{99 103–107} Concerns about the perceived increased difficulty of surgical dissection after pancreatitis, resulting in higher surgical complication rates,^{108 109} and logistical challenges with busy emergency theatre lists^{104 110} have probably contributed to these delays. A recent multicentre RCT* in 266 patients with mild biliary pancreatitis demonstrated that same-admission cholecystectomy reduced the recurrence rate of gallstone-related complications from 17% to 5% as compared with interval cholecystectomy after 4 weeks (RR 0.28, 95% CI 0.12 to 0.66; $p=0.002$).¹¹¹ This included a reduction of recurrent biliary pancreatitis from 9% to 2% (RR 0.27; 95% CI 0.08 to 0.92, $p=0.03$). Same-admission cholecystectomy was not associated with increased technical difficulty or complications and decreased overall costs.^{111 112}

The value of cholecystectomy has also been investigated in acute idiopathic pancreatitis. A multicentre RCT in 85 patients showed that routine elective laparoscopic cholecystectomy reduced the rate of recurrent pancreatitis from 30% to 10% ($p=0.016$) as compared with conservative management. However, since routine EUS was not included in the work-up of (presumed) idiopathic pancreatitis, the treatment effect of cholecystectomy may have been overestimated in this trial. Many patients with presumed

idiopathic pancreatitis patients may in fact have had acute biliary pancreatitis. This was also reflected in the large percentage (59%) of gallbladders in which biliary stones or sludge were found at pathological examination in this RCT.¹¹³

Exocrine and endocrine insufficiency

Due to extensive loss of pancreatic tissue in necrotising pancreatitis, there is a reduction of both endocrine and/or exocrine pancreatic function in 19%–80% of all patients.^{114–117} Awareness on these conditions may support timely treatment in order to prevent complications from diabetes or malnutrition from malabsorption.

Future

This review summarised the best available evidence in acute pancreatitis, mostly based on RCTs. Although many clinical questions have been addressed by RCTs, many questions remain, for instance regarding fluid and pain management but also on the use and timing of interventions such as ERC and the ‘step-up approach’. Besides these important questions, no single RCT has reported on an effective treatment to halt the early sequence of severe systemic inflammation, ultimately leading to multiple organ failure and death in acute pancreatitis. Further innovative studies and RCT’s are needed to find such a treatment and to improve outcomes in acute pancreatitis.

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