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Pancreas (V Chandrasekhara, Section Editor)

New Advances in the Treatment of Acute Pancreatitis

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Abstract

Purpose of review Despite the increasing incidence of acute pancreatitis, the overall mortality of AP has decreased.
Recent findings The findings of recent studies on fluid therapy, analgesics, antibiotics, and enteral nutrition as well as the management of AP complications have led to improvements in clinical care. However, there are still no pharmacologic treatment(s) for AP.
Summary Experimental studies have revealed many potential therapeutic targets, but these will need to be further developed and tested before they can be assessed in randomized controlled trials with important clinical endpoints.

Background

Acute pancreatitis (AP) is the 3rd most common reason for hospitalization among gastrointestinal diseases in the USA, costing $2.6 billion annually [1, 2]. The incidence of AP is increasing in western countries due to the increasing prevalence of obesity and, as a result, biliary sludge and stones [3•]. Despite the lack of pharmacologic treatment(s) for AP, mortality continues to decrease likely due to increased ICU access and management of organ failure (OF) in those with severe AP (SAP) as well as improved management of AP-related complications [3•, 4]. The severity of AP is defined according to revised Atlanta classification [5]. Mild AP is defined as the presence of acute inflammation without necrosis or OF, and is usually self-limited, typically resolving in

1 week. Moderate AP is defined as the presence of the pancreatic necrosis and/or transient OF (≤ 48 h) whereas SAP is defined only as persistent OF (> 48 h) [5].

This review will detail the current evidence-based management of AP, focusing specifically on intravenous fluid resuscitation, analgesics, nutrition, the use of antibiotics, and management of AP complications. We will also discuss potential future pharmacologic therapies.

Why do we not have pharmacologic treatment for acute pancreatitis?

One of the primary limitations of experimental models of AP is their poor correlation with all features of human disease [6]. Therapies are either administered early in the course of AP or at the time of pharmacologic induction of AP in experimental studies; however, in humans, the time from symptom onset to presentation varies and therapies are often administered when patients present to the hospital when pancreatic inflammation is already well-established. Thus, the identification of patients with AP early in their disease course is important so that therapies can be administered at a stage when the inflammatory process can potentially be attenuated. One obvious exception is post-ERCP pancreatitis (PEP) where the time of injury to the pancreas is known and pharmacologic agents can be administered prophylactically. Another critical challenge has been the lack of feasible and meaningful clinical trial endpoints. A recent report from an international symposium on AP showed that the most common primary outcomes of RCTs in AP were mortality in 16% and OF in 15% [7]. However, all of these RCTs have been underpowered to detect differences in these outcomes [8]. The sample size required for an RCT to show differences in persistent OF or mortality would be cost prohibitive [9]. While prognostic scoring systems to predict SAP are commonly utilized as inclusion criteria in RCTs, their low positive predictive value for the development of severe pancreatitis is a strong limitation [10•]. We summarize the limitations of select RCTs in AP in Table 1.

Future clinical trials will need to be standardized with regard to inclusion and exclusion criteria, the impact of supportive care as well as primary and secondary outcomes including clinician and patient-reported outcomes, analgesics requirements, quality of life, and cost-effectiveness.

Fluid therapy

Consensus guidelines have universally recommended aggressive early fluid resuscitation for the management of AP without details regarding the type, volume, and timing of fluid therapy [15, 16]. However, it is worth noting the majority of studies used to support these guidelines have been retrospective which are prone to reverse causation bias. Since patients with SAP are more likely to receive larger volumes of fluid compared to patients with mild AP, it is unknown whether subsequent outcomes are due to volume of fluid administrated or baseline disease severity [17, 18]. Prospective studies are, therefore, required to evaluate the impact of fluid therapy.

There have only been a few RCTs evaluating fluid therapy in AP. Two small RCTs found that lactated Ringer's solution (LR) significantly reduced CRP level and the prevalence of SIRS compared to normal saline (NS) in the first 24–48 h of hospitalization [19, 20]. There are two potential mechanisms related to the benefit seen in LR. First, NS has been shown to increase the risk of hyperchloremic acidosis in critically ill patients which has the potential to

Table 1. Limitation of previous clinical trials

First author, year	Study design	Intervention(s), number of patients	Primary outcome	Limitations
Johnson, 2001 [11]	Randomized trial	Lexipafant, 138 Placebo, 148	Reduction in complication severity of organ failure	Presence of primary outcome in > 40% of patients upon entry into the study
Zhao, 2013 [12]	Randomized trial	NS,40 NS + 6% HES, 40 NS + 6% HES + glutamine, 40	Effectiveness of different resuscitation in severe AP	Critical primary outcomes are not reported, i.e., rates of infected pancreatic necrosis, persistent OF Did not differentiate between transient and persistent OF
Vege, 2015 [13]	Randomized trial	Pentoxifyllin, 14 Placebo, 14	Change in CRP, IL6, IL8, and TNF-α	Difficulty in recruitment 102 of 132 patients approached to discuss the study declined to participate
Buxbaum, 2017 [14•]	Randomized trial	LR Aggressive (20 ml/kg bolus followed by 3 ml/kg/h), 30 Standard (10 ml/kg bolus followed by 1.5 mg/kg/h), 30	Clinical improvement within 36 h including: Decreased hematocrit, BUN and creatinine; improved pain; and tolerance of oral diet	Lack of generalization exclusion of patients with SIRS and/or OF

HES hydroxyethyl starch, *AP* acute pancreatitis, *CRP* C-reactive protein, *IL6* interleukin-6, *TNF* tumor necrosis factor, *LR* lactate Ringer's, *SIRS* systemic inflammatory response syndrome, *OF* organ failure

enhance inflammation and necrosis in AP [21, 22]. Second, LR has a direct anti-inflammatory effect, potentially mediated through macrophage inhibition [23, 24]. A single RCT evaluated the rate of fluid therapy in mild but not moderate or SAP. This RCT showed that early aggressive (20 ml/kg bolus followed by 3 ml/kg/h) fluid administration significantly reduced the time to clinical improvement compared to standard (10 ml/kg bolus followed by 1.5 mg/kg/h) fluid administration with LR [14•]. While the time to clinical improvement may not represent a "hard" trial endpoint, any intervention that reliably reduces the length of hospital stay (LOS) is also important as it would be expected to reduce healthcare costs.

A retrospective study examined the impact of different volumes of fluid administered as a bolus within the first 6 h of ER presentation on outcomes in AP and found that moderate (500–1000 ml) to aggressive (> 1000 ml) fluid bolus was associated with significantly lower rates of invasive intervention(s) (defined as endoscopic and/or surgical drainage or necrosectomy) when compared to nonaggressive fluid bolus (< 500 ml) [25]. The premise of this study was that an early fluid bolus in the ER would not be biased with regard to the

severity of AP. While the study did not establish the optimal fluid bolus volume, the findings do suggest that lower fluid bolus volumes (< 500 ml) should be avoided in the early treatment of AP.

Hypovolemia in AP occurs secondary to insensible fluid losses, lack of oral intake, and capillary leak. Non-ionic colloid fluid preparations including hydroxyethyl starch (HES) have been utilized as fluid therapy in the early stage of AP. Previous RCTs which compared HES to fluids without HES showed no difference in mortality [12]; however, the sample sizes of these RCTs were small and the incidence of other outcomes including necrosis and persistent OF were not reported. Both the FDA and EMA have advised against the use of HES in critically ill patients as several RCTs using HES have failed to show clinically meaningful outcomes [26, 27]. Additionally, RCTs have demonstrated concerning side effects of HES including acute renal failure and pruritus [28, 29].

Several different approaches are recommended to determine whether there is an adequate response to the fluid therapy. The most frequent measurements advocated by International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guideline are heart rate, mean arterial pressure (MAP), urine output (UO), and hematocrit [30]. However, differentiating patients with hypovolemia who will respond to additional fluid is not possible based on the current clinical measurements. A recent small prospective pilot study of 23 patients with SIRS at presentation from China found that aggressive fluid therapy did not appear to change outcomes including mortality, LOS, systemic and local complications, and interventions in patients that were fluid unresponsive (defined as either MAP < 65 mmHg and/or UO < 0.5 ml/kg/h) at 2 and 6–8 h from the time of randomization. This study challenges the utility of MAP and UO as measures of fluid responsiveness in AP [31].

Additional limitations of RCTs evaluating fluid therapy include small sample sizes, patients with variable disease severity, different resuscitation protocols, and varying clinical endpoints [32].

Early nutrition

Enteral nutrition preserves the gut barrier and prevents bacterial translocation. Nutrition is critical in patients with catabolic conditions such as AP [33]. Despite the widespread use of nil per os (NPO) to presumably reduce pancreatic stimulation, the initiation of oral feeding in first 24 h of hospitalization, regardless of disease severity, is now recommended in several guidelines. Oral feeding was shown to be tolerated in 69% of patients with predicted SAP in a recent RCT [34•]. However, if this is not possible or tolerated, then insertion of a nasoenteric tube is reasonable. While recent trials suggest that the early (≤ 48 h after hospitalization) institution of an oral soft, low-fat diet is also associated with a reduced LOS in mild AP [35], it is not clear whether starting an oral diet within 24 h of presentation would positively impact other outcomes in these patients. It is also important that patients tolerate a solid diet by the time of hospital discharge to decrease the risk of 30-day readmission [36].

In patients with SAP, studies have shown that early (< 48 h) enteral feeding is superior to total parenteral nutrition (TPN) [37] and delayed (> 48 h) enteral feeding with regard to rates of infected necrosis, multiple OF, intervention(s), and mortality [38]. There is no difference in outcome between the nasogastric

(NG) and nasojejunal (NJ) routes of administration [39]. NG tubes can be easily inserted at the bedside and are more cost-effective. However, the exclusive role of nasoenteric feeding was recently questioned in an RCT from the Netherlands where patients with predicted SAP were shown to have similar outcomes in terms of mortality and infection when started on an oral diet within 72 h compared to NJ feeding within 24 h of presentation [34•]. A limitation of many prior RCTs of enteral nutrition is that patients with predicted SAP are randomized before it is ascertained that they have actual SAP. It has been shown that current prognostic scoring systems have low positive predictive value for SAP [10•]. In addition, nasoenteric feeding would be expected to benefit patients who have or are developing pancreatic necrosis to prevent local infection as opposed to those with interstitial pancreatitis with persistent OF.

Management of pain

Abdominal pain is the most common and distressing symptom in patients with AP and achieving adequate analgesia is a primary goal of therapy. Several small RCTs comparing different opioid and non-opioid analgesics in patients with AP did not find any particular analgesic to be superior in efficacy or safety [40–42]. A recent Cochrane review of 5 RCTs of 227 patients showed that opioid use in patients with AP reduces the use of additional analgesics without an increased risk of complications [40]. However, a recent experimental study showed that morphine administration worsens the histologic severity of AP and delays inflammatory resolution in mouse models [43]. This finding has not been corroborated in human AP where opioid use is widespread and will need to be further studied.

A trial comparing non-opioid analgesics, intravenous paracetamol, dexketoprofen, and tramadol showed that they were all similar with regard to pain control in AP [41]. A recent trial has demonstrated the efficacy of epidural anesthesia in increasing pancreatic arterial perfusion to improve pain outcomes in patients with AP [44]. The ongoing EPIPAN trial is evaluating clinical outcomes such as the number of ventilator-free days at day 30, OF, mortality, and healthcare-associated costs in critically ill patients with AP receiving epidural ropivacaine and sufentanil vs. standard of care [45]. These trials may help define alternate methods of analgesia in AP.

Management of complications of acute pancreatitis

The development of pancreatic fluid collection(s) is the most common complication of AP. However, more than 70% of acute fluid collections resolve over time and will not require drainage [46]. The approach for symptomatic and/or infected collections is determined by the type of the collection (pseudocyst vs. walled-off necrosis (WON)). While surgical cystgastrostomy or cystjejunostomy was considered the standard for the drainage of pseudocysts for many decades, the advent of endoscopic drainage, particularly through EUS guidance, has been shown to be equally efficacious but associated with less morbidity and cost [47]. A recent review found that endoscopic drainage of pseudocyst(s) was successful in 94% of cases [48].

Combined pancreatic and extrapancreatic necrosis is the most common morphology of necrosis among the patients with AP. The recognition that delaying surgery and other intervention(s) by four or more weeks to allow for

the organization of pancreatic and peripancreatic necrosis has had the greatest impact on reducing mortality [49]. Minimally invasive techniques have been developed for the management of WON, including percutaneous drainage, endoscopic transmural drainage, and minimally invasive retroperitoneal necrosectomy [50]. There have been two RCTs that have compared the outcomes of endoscopic versus surgical drainage [51, 52•]. These trials showed that endoscopic drainage of infected and/or symptomatic WON was as effective as minimally invasive surgery with regard to clinical success. However, a lower rate of pancreatic fistulae and LOS in the endoscopic approach group may result in a shift towards endoscopy as the preferred treatment approach [52•]. A prospective long-term follow-up of 35 patients with SAP showed that non-surgically managed patients also appear to have lower rates of diabetes and exocrine insufficiency as well as lower hospital readmission rates [53].

The challenge of suboptimal drainage of WON using plastic double pigtail stents has been recently overcome with the use of newly designed lumen-apposing metal stents (LAMS). LAMS have a > 90% technical success and their clinical efficacy has been shown in many studies [54–62]. However, as experience with LAMS has increased, a number of studies have reported a number of stent(s)-related adverse events. The risk of adverse events from LAMS includes bleeding (1–7%), perforation (1–2%), stent migration (1–6%), and infection (1–11%) [63]. A recent RCT of 60 patients who underwent endoscopic drainage of WON using either LAMS or double pigtail plastic stents showed no difference with regard to clinical success; however, stent-related adverse events were higher with the use of LAMS (32.3%) when compared to double pigtail plastic stents (6.9%) [64•]. To minimize adverse events with LAMS, patients should undergo follow-up imaging and stent removal within 3–4 weeks if WON has completely or partially resolved. If the WON has partially resolved, it is advised to change LAMS to double-pigtail plastic stents which can remain in situ indefinitely, as many of these patients are at risk of developing disconnected duct syndrome.

Role of antibiotics

Local infection develops in 30% of patients with pancreatic necrosis and results in morbidity and mortality. A recent systematic review showed that the risk of mortality increases more than twofold when pancreatic necrosis becomes infected [65]. However, recent studies evaluating the clinical benefits of prophylactic antibiotics in patients with predicted SAP have not shown any improvement in outcomes. Furthermore, these studies suggest that the mortality (9% vs. 0%, $P = 0.043$) and morbidity (36% vs. 5%, $P = 0.002$) of those treated with prophylactic antibiotics was significantly higher compared with those not treated with prophylactic antibiotics [66]. One potential reason is the development of multidrug-resistant bacteria and fungal superinfection, which is associated with prolonged hospital stay and poor outcomes [66, 67]. The main challenge is that the SIRS due to AP cannot be differentiated from the SIRS of extrapancreatic infection(s).

Previous studies have shown that 34% of AP patients have extrapancreatic infections and administering antibiotics in patients with infected necrotizing pancreatitis reduces morbidity and mortality [68]. It is possible that bacteremia is one mechanism by which pancreatic necrosis becomes infected [69•, 70]. A recent meta-analysis of eight studies showed that conservative management

using antibiotics with or without percutaneous drain insertion resulted in the avoidance of necrosectomy in 64% of patients with infected pancreatic necrosis [71]. However, conservative management was defined as the use of antibiotics and/or percutaneous drainage, the latter of which would not be considered to be "conservative" therapy as drains often require upsizing and changes. Thus, the use of antibiotics should only be reserved for patients with suspected or confirmed infected pancreatic necrosis.

Primary Prophylaxis

Primary prophylaxis after ERCP

A systematic review evaluating the placebo or no stent arms across 188 RCTs comprising 13,296 patients reported an overall incidence of PEP of 9.7% [72•]. In patients at high risk of developing PEP, a landmark RCT showed that rectal indomethacin significantly reduced the incidence of both PEP and severe PEP [73]. This has been further supported by a larger RCT of 2600 patients across 6 centers in China [74] as well as a large retrospective study of rectal indomethacin administration across 4017 patients in the USA [75]. Whether this result is a class effect of NSAIDs is debated as one study showed that rectal diclofenac reduced the incidence of PEP [76] while another study showed that rectal diclofenac and ketoprofen did not [77, 78]. The rectal administration of NSAIDs appears to be crucial, as recent RCTs have shown [79•] that the oral [80], intravascular [78], and intramuscular [81] administration of NSAIDs did not prevent PEP or change the severity and/or pain in comparison to control [69•]. Pancreatic stent placement and rectal NSAIDs are both recommended for preventing PEP in high-risk patients. However, failed pancreatic stent placement can increase the risk of PEP and a secondary analysis of a previous RCT data suggested that prophylactic stent placement may be unnecessary if rectal NSAIDs are administered [82].

The ongoing SVI (Stent vs. Indomethacin) trial is comparing rectal indomethacin alone versus the combination of rectal indomethacin and prophylactic pancreatic stent placement for preventing PEP in high-risk cases [83••]. In patients with average risk of developing PEP, the administration of LR appears to reduce both the incidence and severity of PEP [84•]. Another RCT showed that the combination of LR and rectal indomethacin reduced the incidence of PEP and readmission rates in high-risk patients compared against placebo and NS [85]. However, this trial was markedly underpowered, withholding rectal indomethacin in the true placebo arm raises ethical concerns and the type and rate of fluid administered after ERCP as well as effect of prophylaxis on PEP severity between different groups was not reported. The ongoing Dutch RCT "FLUYT" trial aims to determine the optimal combination of rectal NSAIDs and periprocedural fluid therapy to reduce the incidence of PEP, by studying the type and rate of the fluid therapy (no fluids versus NS versus LR) [86].

Secondary prophylaxis

Management of hypertriglyceridemia

Hypertriglyceridemia accounts for 1–4% of all AP and is seen in patients with primary and secondary disorders of lipid metabolism including excessive alcohol use and poorly controlled diabetes [87]. The risk of AP at triglyceride levels higher than 1000 mg/dl and 2000 mg/dl is 5% and 15%, respectively [88]. A recent epidemiologic study found that even a mild increase in TG levels (> 177 mg/dl) is associated with an increased risk of AP in susceptible patients [89•]. This has implications for patient risk stratification since 25% of the US population has triglyceride levels higher than 176 mg/dl [90]. A recent prospective study suggested that patients with elevated triglyceride (TG) and AP had a higher risk of SAP and more likely required ICU care [91]. Data from large US health databases suggests that maintaining a triglyceride level below 200 mg/dl in patients with severe HTG will proportionally reduce the risk of AP recurrence [92].

AP is associated with major morbidity and mortality in patients with familial chylomicronemia syndrome (FSC) [93]. Traditionally, the treatments for FCS include exceptionally restrictive and low-fat diet as TG lowering medications are insufficient in decreasing TG levels in FCS due to lack of LPL activity [94]. Lifetime compliance with such an extremely fat restrictive diet is difficult and may not normalize TG levels in all patients, and therefore does not prevent the risk of pancreatitis [95].

Management of biliary pancreatitis

In patients with acute biliary pancreatitis, several studies suggest that cholecystectomy reduces the risk of recurrence or other gallstone-related complications [96, 97]. The PONCHO trial, a multicenter RCT from the Netherlands, showed that same-admission cholecystectomy was more effective in preventing the biliary-related complications (16 × 9 to 4 × 7%) and less costly (€234 less) than interval cholecystectomy [98]. In patients with pancreatic necrosis, cholecystectomy should be delayed (about 6 weeks) to reduce risk of complications [15].

Urgent ERCP is not recommended in the setting of cholestasis alone without cholangitis. A meta-analysis of eight RCTs evaluating early ERCP in biliary AP showed that urgent ERCP does not improve clinical outcomes, including mortality and OF [15]. The recently completed APEC trial from the Netherlands randomized 230 patients with predicted severe biliary AP pancreatitis found that early ERCP (performed first 24 h) did not change outcomes including mortality, new-onset OF, or pancreatic necrosis when compared to a conservative treatment strategy where on demand ERCP was performed only if patients developed cholangitis or persistent cholestasis [99•].

Alcohol and smoking cessation

Alcohol and smoking are independently associated with progression to chronic pancreatitis (CP). A recent study suggested that 24% of patients had recurrent AP (RAP) after one episode of alcoholic AP and that cumulative risk of CP is 30% in patients whom smoking and alcohol was the primary risk factor [100]. A previous RCT showed that repeated alcohol cessation counseling compared to single standardized session during hospitalization reduced the development

Table 2. Summary of ongoing clinical studies on potential pharmacologic agents

Pharmacologic agent	Study design	ClinicalTrials.gov identifier	Outcome assessment
GSK3335065 vs. placebo	Phase I Randomized, double-blind, placebo-controlled dose escalation study	NCT03245619	Evaluate safety Evaluate tolerability, pharmacokinetics and pharmacodynamics of single doses
Ketorolac vs. placebo	Phase IV Randomized, placebo-controlled study	NCT02885441	Change in C-reactive protein Organ failure Pancreatic necrosis Mortality
Dexmedetomidine hydrochloride	Phase IV Randomized, placebo-controlled study	NCT02691598	Incidence rate of organ failure Rates of infected pancreatic necrosis
Immunomodulators			
CM4620 injectable emulsion vs. placebo	Phase II Randomized, placebo-controlled study	NCT03401190	CTSI Treatment-emergent adverse events
Thymosin alpha 1 vs. placebo	Early phase I	NCT02473406	Occurrence of pancreatic infection
Monoclonal Antibodies			
Evinacumab vs. placebo	Phase II Randomized, placebo-controlled study of safety and efficacy	NCT03452228	Percent lowering of TG levels from baseline Incidence of anti-drug antibody Incidence of treatment-emergent adverse events Degree of pancreatic injury/inflammation

CTSI CT severity index, *TG* triglyceride

of RAP during a 2-year period [101]. Smoking cessation is extremely challenging in pancreatitis patients; a recent study evaluated smoking cessation in chronic pancreatitis patients and showed that no patients were able to quit after 18 months [102].

Potential future treatments

Cystic fibrosis

The highest expression of CFTR protein in the human body is in pancreatic ductal cells [103]. Pancreas sufficient CF patients have a 22% lifetime risk of AP [104•]. Many pathogenic CFTR variant carriers do not have CF but could be still at risk of

Table 3. Target molecules in treatment of AP

Target molecule	Potential role
IL-1β [109]	Induce trypsin activation Impair autophagy via intracellular calcium changes
Anti-IL-6 antibody [110]	Suppress STAT-3 activation Reduce severity of severe AP
MAP/ERK kinase-1 inhibitor (PD98059) [111]	Protect against cerulein-induced AP
Wortmannin (PI3K pathway inhibitor) [112]	Decrease inflammatory cytokines in SAP

developing pancreatitis, particularly those with bicarbonate-conductance variants [105]. A recent retrospective case series reported that after 3 to 12 months of treatment with ivacaftor, none of the six cystic fibrosis patients had recurrence of pancreatitis. However, this study was limited by a small sample size and limited duration observation [106]. It is also unknown whether patients without cystic fibrosis but whom harbor CFTR variants and develop pancreatitis could benefit from the use of CFTR modulators.

Future directions

Acute pancreatitis leads to a systemic inflammatory response. Many of the therapeutic targets aim to suppress the activation and propagation of the inflammatory response that can ultimately progress to multidrug dysfunction. Therapeutic targets for AP include but are not limited to the inhibition of calcium signaling, serine protease, and TNF-α. Therapeutic agents that block the calcium release-activated channel are currently being evaluated. A phase II study is evaluating DP-b99, a divalent metal ion chelator that can potentially limit the further progression of the disease in those with non-severe AP. Multifunctional acid-resistant serine protease inhibitors such as ulinastatin have been shown to potentially limit serum levels of CRP, IL-6, and TNF-α in patients with AP and improved outcomes in patients with severe pancreatitis [107, 108]. New therapeutic targets are summarized in Tables 2 and 3. Such studies could lead to a promising area of therapeutics for treating patients with AP.

Compliance with ethical standards

Conflict of interest

Mahya Faghih declares that she has no conflict of interest. Christopher Fan declares that he has no conflict of interest. Vikesh Singh reports personal fees from AbbVie, Akcea Therapeutics, Ariel Precision Medicine, and Orgenesis.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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