Pharmacologic management and prevention of acute pancreatitis

Jorge D. Machicado[a] *and Georgios I. Papachristou*[b,c]

Purpose of review
The present article will focus in pharmacologic agents that have been studied to improve acute pancreatitis outcomes, and to prevent the disease at different levels.

Recent findings
Too little and too much early fluid resuscitation can be harmful. The optimal volume, rate, and duration of intravenous fluid therapy is still unknown. Nonopioid analgesics should be the first line of analgesia in patients with acute pancreatitis. A few pharmacologic agents evaluated in acute pancreatitis have resulted in positive pilot trials; however, larger randomized clinical trials (RCTs) are needed before final conclusions. Statin use is associated with lower incidence of acute pancreatitis in the general population and ongoing studies are evaluating its preventive role in acute pancreatitis recurrences. The preventive role of rectal indomethacin in post-endoscopic retrograde cholangiopancreatography pancreatitis is indisputable, with subject selection and timing of administration requiring further investigation.

Summary
There is still no proven effective disease-specific pharmacologic therapy that changes the natural history of acute pancreatitis. New therapeutic targets and pharmacologic agents are in the horizon. Careful refinement in study design is needed when planning future RCTs. There is also a need for drug development aiming at reducing the incidence of the disease and preventing its sequelae.

Keywords
acute pancreatitis, intravenous fluids, medical therapy, natural history, prevention

INTRODUCTION

The pooled annual incidence of acute pancreatitis is 34/100 000 and is rising worldwide [1–3]. As a consequence, acute pancreatitis is one of the leading causes for gastrointestinal-related emergency room visits and hospital admissions in the United States, with direct annual costs of approximately $2.6 billion [4▪]. Most patients have a mild clinical course; however, approximately 20% develop local or systemic complications requiring prolonged hospitalization [5]. Case fatality from acute pancreatitis is approximately 1–2%, but increases to 10% with the development of transient organ failure, 20–30% with persistent single organ failure, 30% with infected necrosis, and reaches 40–60% with persistent multisystem organ failure [5–7]. Following recovery, acute pancreatitis survivors are also at risk for long-term consequences including exocrine pancreatic insufficiency, diabetes mellitus, micronutrient deficiencies, recurrent acute pancreatitis (RAP), chronic pancreatitis, and impaired quality of life [8,9,10▪,11–13,14▪].

Despite significant advances in the field, there is currently no effective disease-specific therapy that changes the natural history of acute pancreatitis. The present review will focus on pharmacologic agents that have been recently studied to improve acute pancreatitis outcomes, and will also provide guidance on pharmacologic primary, secondary, and tertiary prevention. Other treatment approaches such as nutritional, endoscopic, surgical, and

[a]Division of Gastroenterology, Mayo Clinic Health System, Eau Claire, Wisconsin, [b]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania and [c]Division of Gastroenterology, Hepatology and Nutrition, Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Correspondence to Georgios I. Papachristou, MD, PhD, Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Ohio State Wexner Medical Center, 395 W. Twelfth Ave Columbus, Ohio 43210, USA. Tel: +1 614 506 2134; e-mail: Papachristou.2@osu.edu

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KEY POINTS

- There is still no proven effective disease-specific pharmacologic therapy that changes the natural history of acute pancreatitis.
- Too little and too much fluid can be harmful in patients with acute pancreatitis, and the optimal rate, volume, and duration of fluid resuscitation needs further investigation.
- Nonopioid analgesics should be considered the first line of analgesia in patients with acute pancreatitis and only escalated when pain relief is inadequate.
- A holistic preventive approach with pharmacologic interventions aimed at the primary, secondary, and tertiary prevention levels is also needed.

radiologic interventions are beyond the aim of this review and will not be discussed.

PATHOPHYSIOLOGY AND PHARMACOLOGICAL TARGETS

The natural history of acute pancreatitis is closely linked to its pathophysiology. Current consensus is that acinar cell injury results in intra-acinar activation of digestive enzymes, activation of inflammatory transcription factors, and inflammatory cell infiltration [15]. This sequence of events may evolve into systemic inflammatory response syndrome (SIRS), vascular leak syndrome, bacterial translocation from the small bowel, tissue hypoperfusion, pancreatic ischemia/necrosis, and organ dysfunction.

Several pharmacologic agents targeting the above pathogenic events initially showed encouraging results in preclinical studies. However, subsequent randomized clinical trials (RCT) utilizing such agents showed predominantly lack of beneficial effects, or resulted in unpowered or highly biased studies (Table 1) [16▪▪,17–28]. Ongoing registered RCTs are investigating the role of infliximab (Clinicaltrials.gov: NCT03684278), secretin (NCT03686618), indomethacin (NCT02692391, NCT03547232), fecal microbiome transplantation (NCT03015467, NCT02318134), among others. Recent insights in the pathogenesis of acute pancreatitis have provided novel information on the role of impaired autophagy, mitochondrial dysfunction, tryptophan metabolism, calcineurin activation, and excessive calcium influx [29▪▪]. These are potential targets for drug discovery and development, and may impact the future in the pharmacologic management of acute pancreatitis.

CHALLENGES IN PERFORMING RANDOMIZED CLINICAL TRIALS IN ACUTE PANCREATITIS

Generalizability of previous RCTs have been limited by heterogeneity across trials with regards to the selection of study population, timing of randomization or interventions, and definition of outcomes. Traditionally, RCTs included participants with acute pancreatitis at high risk of progressing to severe disease. However, that enrolment strategy was hampered by the suboptimal performance of clinical scoring systems in early ascertaining severe disease

Table 1. Pharmacologic agents evaluated in RCTs and their efficacy in acute pancreatitis

Pharmacologic family	Mechanism of action	Specific agents	Summary of RCTs
Antisecretory agents	Decrease pancreatic enzyme secretion	Glucagon, Calcitonin, Somatostatin and Octreotide	Ineffective
Protease inhibitors	Inhibit serine proteases, complement system, and pro-inflammatory cytokines	Aprotinin, Gabexate, Mesilate, Nafamostat, Ulinastatin	Ulinastatin and intra-arterial infusion of Nafamostat have shown promising results, but benefit is still controversial
Antioxidants	Reduce free radicals	N-acetyl-cysteine, Glutamine, Selenium, Vitamin C and E	Ineffective
Nonsteroidal antiinflammatory drugs	Antiinflammatory effect	Indomethacin suppositories	Insufficient data
Antibiotics and probiotics	Restore gut bacteria and modulate the immune system	Carbapenems, Cephalosporins, Quinolones, and several probiotic species	Ineffective; probiotics are potentially harmful (mesenteric ischemia)
Platelet activation factor antagonists	Modulate immune system	Lexipafant	Ineffective
Activated protein C	Modulate immune system	Drotrecogin Alpha	Insufficient data
Tumor necrosis alpha inhibitor	Modulate immune system	Pentoxifylline	Promising results

[30]. An alternative, but more expensive and tedious approach, would be recruiting all patients with acute pancreatitis irrespective of severity prediction. Such a study would be more feasible with a registry-based clinical trial design utilizing an established multicenter prospective registry platform, such as APPRENTICE [31▪▪].

The effect of any intervention in acute pancreatitis is dependent on its timing of initiation and is limited by a narrow therapeutic window [32]. The inflammatory cascade leading to organ failure is established after 24 h of symptom onset, and therapies administered beyond that timeframe might be ineffective [33]. Previous RCTs using a wide therapeutic window period may have been affected by this confounding factor. For example, in a phase III trial, lexipafant or placebo was initiated in 290 patients with acute pancreatitis within 72 h of symptom onset (<24 h: 24%, 24–48 h: 47%, >24 h: 29%). The study showed no difference in mortality between treatment groups, but after further adjustment by duration of symptoms, the drug was more effective than placebo in decreasing mortality if initiated within the first 24 h of symptom onset [26]. Therefore, early enrolment and randomization are needed in future RCTs of acute pancreatitis , preferably within the first 24 h of symptom onset and when the patients are still in the emergency department.

Another problem in RCTs has been the lack of use of homogenous, replicable, and relevant clinical outcomes. The most commonly used primary outcomes have included mortality, organ failure, infected necrosis, pancreatic necrosis, and SIRS [33]. The development of the Revised Atlanta Classification and the Determinant Based Classification has been a key step towards a more consistent reporting system of clinical outcomes across different studies [34,35]. Another recent promising advancement has been the implementation and validation of the pancreatitis activity scoring system (PASS), which allows for real-time serial assessment of acute pancreatitis activity every 12 h. PASS applies a quantitative weight to five parameters: organ failure, SIRS, abdominal pain, requirement for opioids, and ability to tolerate oral intake [36▪▪,37▪▪].

PHARMACOLOGIC MANAGEMENT OF ACUTE PANCREATITIS

Pharmacologic therapy in acute pancreatitis should aim to: mitigate disease activity, reduce the incidence of local/systemic complications, and/or improve overall survival. We will describe pharmacologic therapies that have suggested efficacy in at least one of those aims.

Intravenous fluids

Intravenous fluid resuscitation has traditionally been considered the mainstay in the treatment of acute pancreatitis. The rationale for early fluid therapy originated from animal studies that demonstrated early inadequate pancreatic vascular perfusion in severe forms of acute pancreatitis [38]. This effect was attenuated by large volume crystalloid infusion in experimental pancreatitis models [39]. Subsequently, human retrospective studies supported the role of early intravenous hydration to reduce in-hospital mortality, organ failure, ICU admission, and hospital stay [40,41]. Therefore, gastrointestinal society guidelines have advocated for the early vigorous fluid resuscitation in acute pancreatitis [42,43].

Fluid administration strategies

Over the last decade, a few studies have reported conflicting results regarding the safety and efficacy of aggressive early fluid resuscitation in acute pancreatitis. In a prospective cohort study, administration of more than 4.1 L of intravenous fluids during the first 24 h of acute pancreatitis was associated with increased risk of persistent organ failure (particularly respiratory and renal) and acute fluid collections [44]. Similarly, a large retrospective multicenter study demonstrated an association of aggressive fluid resuscitation in the first 24 h with increased risk of local complications. However, this study also showed that moderate to aggressive fluid resuscitation in the first 4 h was associated with less need for invasive interventions compared to a non-aggressive approach, without differences in other clinical outcomes [45▪]. These studies have suggested two separate phases of fluid resuscitation: early, during the first 6–12 h of presentation and with a greater impact in outcomes; and late, between 12 and 48 h of presentation and when acute pancreatitis complications may have already developed; thus, aggressive fluid resuscitation could be futile and deleterious (reverse causation bias) [46].

The efficacy of early intravenous fluid resuscitation has been evaluated in a few pilot RCTs. A summary of participants, interventions, outcomes, and results of these RCTs, are presented in Table 2. A RCT from China showed that patients with predicted severe acute pancreatitis on admission randomized to a rapid hemodilution strategy had increased rates of sepsis and mortality, compared to those randomized to a more conservative hemodilution approach [47]. In a RCT from the United States, Wu *et al.* [48] found no difference between a goal-directed and a physician-directed approach with regards to SIRS or CRP levels at 24 h, but the study was too small and underpowered to detect

Table 2. Summary of RCTs comparing different intravenous fluid strategies and fluid types

Author, year	Location	Participants	Interventions compared	Outcomes	Results
Mao, 2010 [47]	Single Center in China	115 with APACHE II score >8, and Hct ≥44% randomized within 24 h of symptom onset	Rapid hemodilution: goal Hct <35% at 48 h Slow hemodilution: goal Hct ≥35% at 48 h	Pancreatic necrosis, sepsis and in-hospital survival	Increased rates of sepsis (79 vs. 58%, $P = 0.016$) and decreased in-hospital survival (66 vs. 85%, $P = 0.02$) in rapid hemodilution arm. No difference in necrosis.
Wu, 2011 [48]	Three centers in USA	40 randomized within 6 h of presentation to ED	4 arms, 2 × 2 factorial design Goal-directed therapy with LR or NS: 20 ml/kg bolus + 3 or 1.5 ml/kg/h Physician-directed with LR or NS: fluids adjusted by treating physician	Primary: 24 h SIRS Secondary: 24-h CRP	No difference between goal-directed vs. physician-directed. LR significantly reduced SIRS (84% reduction vs. 0%, p=0.035) and CRP at 24 h (51.5 vs. 104 mg/dl, $P = 0.02$) compared to NS
Buxbaum, 2017 [49▪▪]	Two centers in USA	60 with predicted mild AP without SIRS, randomized within 4 h of diagnosis	Aggressive therapy: 20 ml/kg bolus +3 ml/kg/h of LR for 12 h Nonaggressive therapy: 10 ml/kg bolus + 1.5 mL/kg/hr of LR	Primary: composite of clinical improvement in pain intensity, oral tolerance, and laboratory tests within 36 h	Increased rates of clinical improvement with aggressive therapy (adjusted HR of 2.3; 95% CI, 1.2–4.5)
Choosakul, 2018 [51▪]	Single Center in Thailand	47 randomized within 1 h of presentation to ED	Goal-directed therapy with LR vs. NS: 20 ml/kg bolus + 3 or 1.5 mL/kg/hr	Primary: 24 and 48 h SIRS	LR reduced 24 h SIRS (26 vs. 4%, $P = 0.02$), but no 48 h SIRS
De-Madaria, 2018 [52▪]	Single Center in Spain	40 randomized within 24 h of symptom onset	LR vs. NS: patients with haematocrit >44%, SIRS, hypovolemia, and/or BUN >20 mg/dl received 15 mL/kg bolus + 1.2 mL/kg/h. Otherwise, 10 ml/kg bolus + 1 ml/kg/h	Primary: 24, 48, and 72 h SIRS; 48 and 72 h CRP	LR reduced 48 and 72 h CRP levels ($P < 0.05$), but did not reduce SIRS

BUN, blood urea nitrogen; CRP, C-reactive protein; ED, Emergency department; Hct, hematocrit; LR, lactated Ringer's solution; NS, normal saline; SIRS, systemic inflammatory response syndrome.

differences in other relevant clinical outcomes. Finally, in another recent RCT from the United States, patients with predicted mild acute pancreatitis randomized to an aggressive fluid resuscitation strategy resulted in a greater rate of clinical improvement, and lowered the risk of hemoconcentration, development of SIRS, and persistent SIRS [49▪▪]. From these studies, we can conclude that too little and too much fluid is likely harmful in acute pancreatitis , and precise determination of the volume, rate, and duration of intravenous fluids needs to be further delineated.

Type of fluid

The use of colloids may increase the risk of multisystem organ failure in acute pancreatitis, so crystalloids are currently the standard of care for fluid resuscitation [50▪▪]. Three small RCTs have shown reduction of SIRS and CRP with lactated Ringer's solution compared to isotonic saline [48,51▪,52▪]. These studies were not powered to detect an effect in other relevant clinical outcomes, such as mortality and local or systemic complications (Table 2). A theoretical benefit of lactated Ringer's solution is that it may carry an antiinflammatory effect, reduce trypsin activity, and lower pancreatic acidosis [52▪].

Analgesics

The importance of abdominal pain has been recently emphasized in the development of the PASS disease activity index, which includes categories for severity of pain and intravenous morphine equivalent dose [36▪▪,37▪▪]. In the acute setting, pain is typically managed with parenteral analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs), local anesthetics, and opioids. In an Italian survey study of 840 patients with acute pancreatitis, NSAIDs were administered in 55%, tramadol in 26%, opioids in 4%, and a combination of different drugs in 14% [53]. In the United States, the utilization of opioids in acute pancreatitis is significantly higher than in other regions of the world (93 vs. 51%) [54]. Quality of the evidence to support one analgesic strategy over the other is low and a systematic review of eight RCTs did not clearly favor any specific analgesic agent [55]. Of particular interest is that opioids did not outperform NSAIDs (metamizole) in the only RCT that

compared both interventions in patients with acute pancreatitis [56]. We recommend nonopioid analgesics to be considered as the first line of analgesia in patients with acute pancreatitis and only escalated when pain relief is inadequate.

Antibiotics

Infections are a common complication following acute pancreatitis and are associated with increased mortality [5]. Approximately one third of patients with necrotizing pancreatitis develop infected pancreatic necrosis (IPN). In addition, about one third of all patients with acute pancreatitis develop extrapancreatic infections, such as pneumonia and bacteremia [57]. However, neither prophylactic antibiotics or probiotics have demonstrated significant reduction in mortality or in the incidence of IPN [50▪▪,58,59]. As a consequence, antibiotic therapy is reserved to patients with acute pancreatitis with suspected or proven IPN, and to those with acute cholangitis or extra-pancreatic infections [60].

Promising pharmacologic agents

Among the myriad of pharmacologic agents evaluated in RCTs for acute pancreatitis, a few are worth mentioning given their promising results. Systemic intravenous ulinastatin (a protease inhibitor) was compared to placebo in a multicenter RCT of 135 patients with acute pancreatitis of any severity, and significantly prevented development of organ failure and reduced mortality in patients with severe acute pancreatitis by APACHE-II score [20]. Continuous regional arterial infusion (CRAI) of nafamostat (a protease inhibitor), administered via a catheter placed into a feeding artery to the pancreas in a RCT of 79 patients with severe acute pancreatitis demonstrated reduction of mortality and need for surgical interventions in comparison to placebo [21]. Although CRAI has been approved in Japan, its benefit is still controversial and is not recommended in any other country [22]. Oral pentoxyfilline (a nonselective phosphodiesterase and tumor necrosis factor-alpha inhibitor) reduced ICU admissions, and shortened ICU and overall hospital stay compared to placebo, in a single center pilot RCT of 28 patients with acute pancreatitis [28]. Overall, the results of these RCTs are promising, but large scale and well designed RCTs are required before implementing any of these pharmacologic agents in clinical practice.

PHARMACOLOGIC PREVENTION OF ACUTE PANCREATITIS

Given the epidemiological burden of acute pancreatitis and its long-term sequelae, a comprehensive preventive approach has recently been developed [61▪▪]. In primary prevention, pharmacologic interventions are applied to the general population or to high-risk individuals, with the aim of decreasing acute pancreatitis incidence. Secondary prevention in acute pancreatitis involves in-hospital management, removal of known causes, and prevention of progression into RAP or chronic pancreatitis. Finally, tertiary prevention aims at minimizing resulting sequelae of acute pancreatitis.

Primary prevention in the general population

Data on primary pharmacologic prevention of acute pancreatitis at a population level is limited to statins. Statins were traditionally linked to drug-induced acute pancreatitis in early studies. However, a case–control study and a meta-analysis of large RCTs with cardiovascular endpoints suggested that statins were associated with a lower risk of developing acute pancreatitis [62,63]. Since then, additional population and cohort studies have demonstrated an independent association of statin use with lower incidence of acute pancreatitis, milder disease course, and decreased mortality [64,65,66▪]. There are no traditional RCTs evaluating statin use at a population level, and such studies would be extremely difficult to perform because of the large sample size needed.

Primary prevention in high-risk individuals

Conducting RCTs in primary prevention is more feasible in high-risk individuals than in the general population. Individuals undergoing endoscopic retrograde cholangiopancreatography (ERCP) have an overall risk up to 10% in developing post-ERCP pancreatitis (PEP) [67]. At least 20 published RCTs have evaluated the efficacy of rectal NSAIDs, and meta-analyses demonstrated a rate of PEP reduction between 40 and 60% [68,69,70▪]. There is a growing body of literature regarding patient selection and timing for administration of rectal NSAIDs [69,71–74,75▪]. The role of indomethacin alone versus indomethacin with pancreatic stent placement is currently being investigated in a large multicenter RCT (NCT02476279). With regards to peri-procedural intravenous fluid administration, a meta-analysis of RCTs has also demonstrated that administration of lactated Ringer's solution reduces the risk of PEP by 50% [76▪]; however, additional data are necessary to define the optimal infusion rate and fluid volume. Other promising agents for preventing PEP that are currently under investigation include sublingual nitroglycerin, nafamostat, magnesium, calcineurin inhibitors, statins, and hemin [77].

Another example of primary prevention in a high-risk population occurs in hypertriglyceridemic pancreatitis. Traditionally, a triglyceride level greater than 1000 mg/dl was associated with acute pancreatitis; however, a recent large Danish population study suggested that the risk increases at levels as low as 177 mg/dl [78]. Future studies are needed to assess whether lowering the current thresholds (500 mg/dl) of initiating triglyceride-lowering agents will be effective in reducing the risk of acute pancreatitis [79].

Secondary prevention

Other than removing or controlling the etiologic factors related to an attack of pancreatitis, there are no approved medications that prevent the progression of acute pancreatitis to RAP or chronic pancreatitis. Pharmacologic interventions for smoking and alcohol cessation should be considered in patients who fail conventional approaches, but have not been well studied in the context of preventing acute pancreatitis progression [80,81]. An ongoing RCT is currently enrolling patients with RAP to determine the efficacy of simvastatin in preventing pancreatitis recurrences (NCT02743364) [82▪▪]. Identifying targetable pathogenic pathways and early biomarkers of disease progression including those regulating inflammation and fibrosis will be of paramount importance to accelerate the drug discovery pipeline [83,84].

Pharmacologic tertiary prevention

This includes the pharmacologic management of postpancreatitis diabetes mellitus, exocrine insufficiency, and micronutrient deficiencies [61▪▪]. Current practice mainly involves insulin administration, pancreatic enzyme supplementation, and micronutrient replacement. For pain relief, it is recommended to use a stepwise escalation of analgesic drugs with increasing potency until pain relief is obtained.

CONCLUSION

There is still no proven effective disease-specific pharmacologic agent that alters the natural history of acute pancreatitis. Supportive therapy with early adequate fluid resuscitation is still the gold standard. Large-scale well designed studies are needed to clarify the optimal rate, duration, volume, and fluid type for early resuscitation. New therapeutic targets and pharmacologic agents are in the horizon, but refinements in the design of future RCTs are needed. A holistic preventive approach with interventions aimed at the primary, secondary, and tertiary prevention levels is imperative. Future drug development should target each of these prevention levels aiming to reduce the incidence of the disease and decrease its progression into more advanced pancreatitis stages such as RAP and chronic pancreatitis.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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