EXPERT REVIEWS

Treating acute pancreatitis – what's new?

Expert Rev. Gastroenterol. Hepatol. Early online, 1–11 (2015)

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The medical treatment of acute pancreatitis continues to focus on supportive care, including fluid therapy, nutrition, and antibiotics, all of which will be critically reviewed. Pharmacologic agents that were previously studied were found to be ineffective likely due to a combination of their targets and flaws in trial design. Potential future pharmacologic agents, particularly those that target intracellular calcium signaling, as well as considerations for trial design will be discussed. As the incidence of acute pancreatitis continues to increase, greater efforts will be needed to prevent hospitalization, readmission and excessive imaging in order to reduce overall healthcare costs. Primary prevention continues to focus on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and secondary prevention on cholecystectomy for biliary pancreatitis as well as alcohol and smoking abstinence.

KEYWORDS: acute pancreatitis • clinical trials • drugs • medical therapy • primary prevention • resource utilization • secondary prevention

General issues

Over the last several decades, significant advances have been made in understanding the key pathophysiologic mechanisms of acute pancreatitis. However, the treatment of acute pancreatitis continues to be supportive as there are no effective pharmacologic therapies available. Prior randomized controlled trials (RCTs) evaluated antisecretory agents, protease inhibitors (PIs), immunomodulators, antioxidants and anti-inflammatory agents for the treatment of acute pancreatitis [1]; however, none of these have proven to be effective in reducing morbidity and mortality. This review will focus on the shortcomings of prior pharmacologic therapies, clinical trial design issues, and current supportive care in acute pancreatitis.

There are many potential reasons for the lack of an effective pharmacologic agent for the treatment of acute pancreatitis. These can be largely categorized as related to the pharmacologic agent or trial design.

Experimental models of acute pancreatitis share little homology with human disease; therefore, the benefits seen with some therapeutic agents in experimental studies have not translated to human clinical trials [2–4]. As with many systemic inflammatory diseases, acute pancreatitis is associated with an initial insult that subsequently triggers monocyte and neutrophil migration as well as complex cascade of inflammatory mediators and cytokines. Prior agents likely acted at more downstream points in the inflammatory cascade and, therefore, were not shown to be effective. An exception to this was the immunomodulator, lexipafant, an antagonist of the platelet activator factor, which is a proinflammatory cytokine that contributes to the development of the systemic inflammatory response syndrome (SIRS). However, the pivotal trial of lexipafant did not show a benefit in patients with predicted severe acute pancreatitis [5]. It is certainly possible that agents that block cytokines and other inflammatory mediators are also still too far downstream to have a beneficial effect. Another problem is the difficulty in differentiating SIRS due to acute pancreatitis from SIRS due to sepsis and the fact that these two processes can be concurrent in the same patient. Therefore, agents shown to be effective for treating experimental acute pancreatitis may not have had the same effect in human clinical trials where SIRS may have been due to an extrapancreatic infection. Extrapancreatic infections in acute pancreatitis were reported to be as high as 24% in one study [6] and these carry mortality rates equivalent to infected necrosis alone [7]. Monocyte activity has been shown to be different in SIRS due to

 10.1586/17474124.2015.1048225 ISSN 1747-4124

sepsis versus acute pancreatitis and this may represent a potential therapeutic target [8].

There are several design limitations of prior RCTs of pharmacologic agents. The RCT evaluating lexipafant highlights many critical issues that will need to be addressed for the study of any future agents. This trial randomized 290 patients with predicted severe acute pancreatitis (APACHE II score ≥6) and whose symptoms started within 72 h with the primary outcome of new-onset organ failure [5].

The first issue is patient selection. Since nearly 85–90% of patients with acute pancreatitis have mild uncomplicated disease that rapidly improves with supportive care, the focus of new therapies has largely been on patients either with predicted severe acute pancreatitis or with actual severe acute pancreatitis. While there has been extensive debate about whether persistent organ failure and/or infected necrosis should define actual severe acute pancreatitis [9], it should be noted that the incidence of and mortality attributed to infected necrosis appear to be decreasing, likely due to the combination of early enteral nutrition to preserve the intestinal barrier [10], antibiotics to treat extrapancreatic infections thus avoiding 'seeding' of necrosis [11], utilization of less surgical necrosectomy over time [12], and the use of percutaneous drain insertion with a 'step-up' to minimally invasive endoscopic and surgical approaches for necrotizing pancreatitis [13]. A substantial body of research has been conducted to develop clinical and radiologic scoring systems that identify those patients at risk of severe acute pancreatitis as early as possible during their hospitalization. The primary limitation of these scoring systems is their poor positive predictive value for severe acute pancreatitis, ranging from 11 to 23% if severe acute pancreatitis is defined as persistent organ failure [14]. In other words, most patients who have predicted severe acute pancreatitis early in their hospital course do not ultimately develop severe acute pancreatitis. This was highlighted in a recent trial of 205 patients with predicted severe acute pancreatitis (APACHE II score ≥8, Imrie/modified Glasgow ≥3 or C-reactive protein (CRP) >150 mg/l) who were randomized to early nasoenteric versus oral feeding but only 20% of the patients developed either persistent single or multiple organ failure [15]. While 63% of the patients in this study developed necrotizing pancreatitis, only 12% of patients developed infected necrosis which is a more important marker of severe acute pancreatitis than sterile necrosis. This trial, in essence, randomized a large number of patients who developed mild acute pancreatitis and in whom enteral nutrition is not indicated.

The lexipafant trial defined predicted severe acute pancreatitis by an APACHE II score of ≥6 and severe acute pancreatitis by the Atlanta classification, which included any local complication (pseudocyst, abscess or necrosis) as well as any duration of organ failure consistent with severe acute pancreatitis. The primary outcome of the trial was the rate of complications and the sample size was calculated on the assumption that there would be a 40% relative risk reduction from 40 to 24% [5]. According to the Atlanta classification, 61% of the patients in the study had either organ failure and/or a local complication during their hospitalization; however, 44% of patients had organ failure (the primary outcome) at the time of randomization. Only 14% developed new onset organ failure and the rates did not differ between the two arms of the trial (27% in placebo vs 22% in lexipafant group). These rates are below the expected frequency of complications and this suggests that the study was, in fact, underpowered. It is also important to note that a relative risk reduction of 40% is overly optimistic for any drug in the treatment of acute pancreatitis, particularly if primary outcome was new-onset organ failure. If the trial was powered using the scoring system with the highest positive predictive value (23%) for predicting persistent organ failure [14], a sample size of 10,132, 1524, and 336 would be required to demonstrate a relative risk reduction of 10, 25 and 50%, respectively, in a randomized control trial of an investigational drug versus placebo assuming an $\alpha = 0.05$, $\beta = 0.20$ and power = 0.8.

The most suitable measures or outcomes to assess therapeutic response to a potential drug for acute pancreatitis are not clear. Unlike inflammatory bowel disease, there is no Crohn's disease activity index that could be routinely utilized in clinical trials to evaluate efficacy and meet established regulatory guidelines in acute pancreatitis. There was a consensus conference at the recent annual American Pancreatic Association meeting to discuss the creation of a disease activity index for acute pancreatitis [16]. The large sample sizes required to assess 'hard' outcomes such as persistent organ failure, necrosis or mortality are all prohibitive outside of a costly, long-term multi-center study (Table 1). The use of persistent SIRS as a measure of response to therapy has been advocated by professional societies [17] as it occurs in 18–30% of patients [18–22], is easy to calculate, can be performed frequently, and is a clinical reflection of the underlying inflammatory process. More importantly, persistent SIRS has very high negative predictive value for severe acute pancreatitis, that is, the absence of persistent SIRS is highly associated with mild acute pancreatitis. While the positive predictive value of SIRS for persistent organ failure was only 11% in the validation group of one study [14], another recent study found that persistent SIRS had a positive predictive value of 80% for developing at least one of the following: need for intensive care unit (ICU), persistent organ failure, any organ failure, fluid collection, necrosis, need for intervention or death [18]. Therefore, any drug that significantly reduces the rates of persistent SIRS would be expected to reduce the rates of important outcomes such as persistent organ failure and mortality. In addition, persistent SIRS is associated with increased resource utilization and costs due to the increased use of imaging, antibiotics and interventions as well as longer length of stay.

Another issue is that by the time most patients with acute pancreatitis present to the emergency room, the inflammatory cascade has progressed to the point where any therapy will no longer be effective. This was also highlighted in the lexipafant trial, where approximately 25 and 50% of patients presented within 24 h and between 24–48 h of symptom onset,

Table 1. Total sample size requirements for a randomized controlled trial of an investigational drug versus placebo based on the expected prevalence of various outcomes and the expected relative risk reductions.

Outcome (estimated prevalence in acute pancreatitis)	Expected relative risk reduction					
	10%	*20%*	*25%*	*30%*	*40%*	*50%*
Persistent SIRS (20%)	12,078	2894	1810	1228	658	398
Necrosis (10%)	26,990	6426	4008	2710	1442	868
Persistent organ failure (5%)	56,816	13,490	8404	5676	3012	1810
Mortality (1% in all patients with acute pancreatitis)	293,422	70,002	43,566	29,396	15,570	9346
Mortality (30% in severe acute pancreatitis)	7106	1716	942	734	396	240

Calculation based on standard parameters used in sample size estimates for randomized clinical trials ($\alpha = 0.05$, $\beta = 0.20$, power 0.8).
SIRS: Systemic inflammatory response syndrome.

respectively, but the earlier presentation did not result in an impact on reducing new-onset organ failure. This suggests that the correlation between the natural history of the inflammatory cascade and clinical manifestations of acute pancreatitis, that is, abdominal pain, is not well understood.

What agents hold promise as we move forward?

An increase in the intracellular concentration of calcium followed by an increase in calcium entry from the interstitium in acinar cells are important steps in the pathogenesis of acute pancreatitis as this results in protease activation, inflammation and necrosis [23]. There are three potential targets for therapy. The first is decreasing the intracellular concentration of calcium. A lipophilic calcium chelator, DP-b99, previously evaluated in acute ischemic stroke without efficacy [24], is currently being studied in a Phase II clinical trial in Eastern Europe where patients with predicted severe acute pancreatitis, who present within 48 h of symptom onset, are randomized to either 2 days of DP-b99 or placebo [25]. The primary outcome of the study is CRP levels on day 6. The second is preventing intracellular calcium release from the endoplasmic reticulum and zymogen granules, which is mediated by the inositol 1,4,5-triphosphate receptor. It has been shown that calmodulin activation by CALP3 can prevent an increase in the intracellular calcium concentration by inhibiting inositol 1,4,5-triphosphate receptor [26]. The third is preventing calcium entry by blockade of the Ca^{2+} release-activated Ca^{2+} channels in the acinar cell plasma membrane. A recent study demonstrated the efficacy of the Ca^{2+} release-activated Ca^{2+} channel blocker, GSK-7975A, in inhibiting protease activation and necrosis [27].

Complement and contact system activation is known to occur in acute pancreatitis and can result in inactivation of C1 esterase inhibitor due its increased turnover under inflammatory conditions [28]. Early experimental studies showed a benefit to using C1 esterase inhibitor for prophylaxis [29] but not therapy [30] of acute pancreatitis. The first report of a clinical benefit of C1 esterase inhibitor was demonstrated in two pediatric patients who developed acute pancreatitis after undergoing allogeneic stem cell transplantation for hematologic malignancies [31]. This was followed by reports of two patients with acute pancreatitis due to hereditary angioedema successfully treated with C1 esterase inhibitor [32,33]. Recombinant C1 esterase inhibitor is currently US FDA approved for treatment of hereditary angioedema.

Primary prevention

Since the time of injury is known in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), there has been interest in the pharmacologic and non-pharmacologic prevention of post-ERCP pancreatitis (PEP) since late 1970s. While the pathophysiology of PEP is incompletely understood, there is general acceptance that papillary trauma during ERCP results in edema and pancreatic outflow obstruction. The demographic, clinical and procedural risk factors for PEP are well established and most prior RCTs have focused on employing prophylaxis in high-risk patients [34]. Based on a systematic review of the placebo or no stent arms of 108 RCTs involving 13,296 patients, the incidence of PEP was 9.7 and 14.7% in average and high-risk patients, respectively [35].

At the present time, there are two widely used methods for the prevention of PEP in high-risk patients: pancreatic stent placement and rectal NSAIDs. In a recent meta-analysis of 14 RCTs of 1541 patients, there was a 61% reduction in the risk of developing PEP in patients randomized to pancreatic stents versus no stenting and the benefit was noted in all severity subgroups [36]. While a meta-analysis of four RCTs demonstrated a pooled relative risk of 0.36 (95% CI: 0.22–0.60) for PEP in patients receiving rectal NSAIDs [37], widespread utilization of this practice was limited until a landmark trial of rectal indomethacin, administered just after ERCP, versus placebo demonstrated a statistically significant difference between the rates of PEP (9.2 vs 16.9%) and severe PEP (4.4 vs 8.8%) in the two groups, respectively [38]. Critics of this study contended that over 80% of patients were at very high risk, due to suspected sphincter of Oddi dysfunction and most of these received pancreatic stents. However, the efficacy, safety, and cost-effectiveness of rectal NSAIDs have led to the recommendation of their use in all patients undergoing ERCP. A *post hoc* regression analysis of the subgroups from the original RCT by Elmunzer *et al.* suggested that rectal indomethacin may be

doi: 10.1586/17474124.2015.1048225

associated with greater reductions of PEP than pancreatic stents alone or the combination of pancreatic stents and rectal indomethacin [39]. This has stimulated interest in exploring the use of one or more pharmacologic agents in combination and possibly forgoing pancreatic stent placement for the prevention of PEP. The combination of sublingual nitrates and rectal indomethacin was shown to be superior to rectal indomethacin alone for PEP prophylaxis in a recent trial of average to low risk patients undergoing ERCP [40]. There is also an ongoing trial evaluating papillary spray of epinephrine and rectal indomethacin versus rectal indomethacin alone for PEP prophylaxis in high risk patients [41]. Papillary application of epinephrine is associated with local vasoconstriction, which prevents papillary edema and pancreatic outflow obstruction. Epinephrine was shown to be the most effective agent out of 16 drugs for preventing PEP in a network meta-analysis of 99 RCTs evaluating 25,313 patients, potentially because its mechanism of action is the 'pharmacologic equivalent' of a pancreatic stent [42].

Enrolling the highest risk patients will become more challenging in PEP prophylaxis trials as ERCP will be used less frequently for treating sphincter of Oddi dysfunction given the lack of difference in abdominal pain between those randomized to sphincterotomy versus sham in the recently completed EPISOD study [43]. This will reduce the number of patients who are deemed to be high risk by patient-related factors; therefore, procedural factors will largely govern designation as 'high risk' for PEP.

Resource utilization

As nearly 85–90% of patients with acute pancreatitis have mild disease where simple supportive measures lead to symptomatic improvement and discharge within days of hospital admission, a trial from Turkey randomized 84 patients with mild predicted acute non-alcoholic pancreatitis to either continued hospitalization or home monitoring with periodic visits by a nurse. They found no differences in the rates of readmission, development of severe disease, or time to resolution of abdominal pain and re-initiation of oral feeding between the groups [44].

While professional society guidelines recommend avoiding imaging in patients who fulfill the clinical and laboratory criteria for a diagnosis of acute pancreatitis and using it only in patients who are not clinically improving or in whom the diagnosis is in question at the time of presentation [17,45], there is a clear trend towards the overutilization of imaging without a corresponding improvement in outcomes [46–48]. Among patients with severe acute pancreatitis, there is an even greater utilization of CT imaging with concerns raised regarding cumulative radiation exposure [49,50].

Readmissions occur in 19–33% of patients with acute pancreatitis [51–54]. This contributes to increased costs and will be a factor for payment in the future. The strongest factors predicting readmission in acute pancreatitis are ongoing gastrointestinal symptoms, discharge from hospital without tolerating at least a soft diet, pancreatic necrosis, antibiotic use and moderate-to-heavy alcohol use [51,52]. A three-tiered scoring system was developed using these risk factors and tested in a derivation and validation cohort, where the highest risk patients had a 30-day readmission rate of 87 and 68%, respectively [52].

Diagnosis of pancreatic necrosis

While several imaging techniques, including perfusion CT [55,56] and radiolabeled ammonia PET CT [57], have been developed in an effort to more accurately diagnose early pancreatic necrosis over contrast-enhanced CT, there are several reasons why the delineation of pancreatic necrosis early in the course of hospitalization does not change management. First, it is the presence of early persistent SIRS and/or persistent organ failure, not pancreatic necrosis, that dictates transfer to an ICU. Early persistent organ failure is the primary determinant of mortality in the first 1–2 weeks of hospitalization. The mortality associated with infected pancreatic necrosis usually occurs after this time. Second, early clinical and radiologic scoring systems are equivalent for determining prognosis of acute pancreatitis [58]. Therefore, a CT scan on admission is not required for the assessment of disease severity. Third, the lack of specific treatment for sterile pancreatic necrosis makes the early diagnosis of this condition less relevant for clinical management. CT scans should be reserved for those patients who fail to improve clinically [59].

Secondary prevention

The prevention of additional episodes of acute pancreatitis after an index episode of acute pancreatitis is important and dependent on etiology. Since recurrent biliary events are as high as 18% with interval cholecystectomy [60], cholecystectomy prior to hospital discharge is recommended in patients with mild acute biliary pancreatitis [61]. Endoscopic sphincterotomy alone is controversial, with some studies reporting an increased rate of recurrent biliary complications [62,63] and others a decrease [64,65]. However, the optimal timing of cholecystectomy in mild biliary pancreatitis will be addressed by a randomized trial currently underway in the Netherlands [66]. Cholecystectomy should be delayed in patients with severe acute biliary pancreatitis, particularly those with large fluid collections, until these have resolved but the strength of the evidence for this is weak [67].

While alcoholic pancreatitis occurs in only 4% of patients who drink heavily, it represents the second most common cause of acute pancreatitis and carries a large economic burden to the healthcare system. It is clear that patients who abstain from alcohol after an index episode of acute pancreatitis can prevent recurrent episode(s) of acute [68,69] and the development of chronic pancreatitis [70,71]. This suggests that greater effort should be put into place to more intensively counsel patients about the benefits of abstinence that might require the assistance of psychiatrists with substance abuse expertise [72]. The role of smoking in pancreatitis has also been further clarified with large prospective cohort studies showing an increased risk of acute [73] and acute recurrent pancreatitis [74] with smoking

in a dose-dependent manner, even after adjusting for alcohol use and body mass index.

Fluid therapy

While consensus and professional society guidelines have invariably argued for the use of 'aggressive' fluid therapy in acute pancreatitis [45], data from prior studies have shown conflicting results, with some showing a benefit and others harm [75]. There are several potential reasons for the variability of findings. First, the design of retrospective studies cannot distinguish between 'cause' and 'effect' of aggressive fluid therapy, that is, it is not known whether the development of adverse outcomes (persistent SIRS, persistent organ failure and pancreatic necrosis) compels the clinician to administer aggressive fluid therapy or aggressive fluid therapy is administered and prevents these adverse outcomes [76]. Second, there may be a 'therapeutic window' in which aggressive fluid therapy would potentially reverse or attenuate the inflammatory cascade but it is missed in many patients because of the variability in the time between the onset of symptoms and presentation to the hospital [77]. Third, the vascular permeability that results in third spacing in acute pancreatitis does not resolve simply by the administration of aggressive fluid therapy. A few studies have explored the use of colloid fluids, including dextran [78] and hydroxyethyl starch [79], in an effort to increase plasma oncotic pressure and prevent third spacing. However, a recent systematic review showed increased mortality in critically ill patients receiving hydroxyethyl starch [80,] whereas an RCT comparing albumin and saline in ICU patients did not show any differences in outcomes but it is not known how many had acute pancreatitis and albumin is expensive [81]. Agents that directly target vascular leak may prove to be more beneficial than those that augment plasma oncotic pressure. Experimental studies have shown that endothelin receptor blockade can reduce vascular leak in acute pancreatitis [82] and this appears to be more effective than PAF antagonists and intracellular adhesion molecule-1 antibody [83].

It has long been recognized that >6 l of fluid sequestration at 48 h is a poor prognostic sign [84]. A recent study found that younger age, an alcoholic etiology, hemoconcentration, hyperglycemia and SIRS at presentation were all predictors of increased fluid sequestration at 48 h as those with increased sequestration are at a significantly increased risk of developing acute fluid collections, necrosis and persistent organ failure [85]. These may be helpful for identifying patients, early in their course, who may benefit from the combination of aggressive fluid therapy and agents that prevent vascular leak.

Recent guidelines from a joint meeting of the IAP/APA in 2013 provide clinicians with detailed recommendations for type and rate of crystalloid administration as well as measures to follow to assess for response to therapy in acute pancreatitis [17]. They advocate for administering fluid at a rate of 5–10 cc/kg/h and the use of lactated Ringer's based on a trial that demonstrated significantly lower CRP levels and SIRS at 24 h with the use of lactated Ringer's compared to saline [86]. The measures to assess response to therapy include heart rate, mean arterial pressure, urine output, hematocrit (goal 35–44%), and BUN (goal <20 mg/dl). They also recommend using invasive monitoring of intravascular volume status in ICU patients.

Nutrition

Bowel rest is one of the therapies commonly utilized to treat acute pancreatitis. This is effective for the treatment of patients with mild acute pancreatitis as they can rapidly advance their diets after a few days of hospitalization when their abdominal pain has improved off analgesics, bowel sounds are present and feelings of hunger are reported. Immediate refeeding in patients with mild acute pancreatitis can lead to refeeding intolerance [87,88], most commonly defined as recurrent abdominal pain, in 12–25% of patients [87–89].

While a liquid diet has been most commonly used for refeeding after fasting, the data to support this practice are limited. A meta-analysis of three RCTs with 326 patients with mild acute pancreatitis showed that a solid diet reduced the length of hospital stay, compared to a liquid diet, but did not affect the rates of recurrent pain after refeeding [90]. Decreased length of hospital stay has also been shown in the most recent RCTs with a solid as opposed to a liquid diet in mild acute pancreatitis [91,92]. One recent RCT compared early nasogastric tube feeding to nothing *per os* in patients with mild-to-moderate acute pancreatitis and found that the patients in the nasogastric tube feeding group had significantly less abdominal pain, need for opiates and refeeding intolerance but did not decrease length of stay [93]. However, given the costs of and aversion to nasogastric tube insertion by patients, this is unlikely to be widely adopted into clinical practice.

Patients with severe acute pancreatitis are typically left on bowel rest for extended periods of time, especially since refeeding intolerance is high [94]. However, gut barrier dysfunction is common in severe acute pancreatitis and can result in SIRS as well as systemic and pancreatic infection due to the translocation of bacteria across the intestinal mucosa [95]. Gut barrier dysfunction, as measured by tests that assess gut epithelial barrier (e.g., intestinal fatty acid binding protein) and function (e.g., lactulose/mannitol ratio, D-xylose, and serum diamine oxidase) as well as bacterial translocation (e.g., endogenous antiendotoxin antibodies), is found in nearly 60% of patients in acute pancreatitis based on a recent meta-analysis of 44 prospective clinical studies [96]. Early experimental studies demonstrated that early jejunal feeding improves gut barrier function and prevents bacterial translocation [97,98]. A meta-analysis of eight RCTs of 381 patients with severe acute pancreatitis showed significantly lower rates of mortality, organ failure, infection, and surgical intervention in those randomized to enteral versus parenteral nutrition [99]. While the nasojejunal route has been the preferred method for enteral feeding, there are no data to support its superiority over the nasogastric route [100]. There is also no evidence to support the use of one enteral formulation (e.g., polymeric vs elemental) over another

doi: 10.1586/17474124.2015.1048225

due to the overall low quality of prior trials [101]. A meta-analysis of 11 studies and recent retrospective study demonstrated that the initiation of early (<48 h) enteral nutrition was associated with less infection and mortality in patients with severe acute pancreatitis [102,103]. One prominent limitation in these retrospective studies stems from cause and effect as it is quite possible that enteral nutrition was more frequently delayed in patients with more severe illness. The timing and route of nutrition has been called into question by the results of the recently published PYTHON trial [15] which randomized patients with predicted severe acute pancreatitis to nasojejunal feeding within 24 h or an oral diet after 72 h of presentation and found no differences using a primary composite outcome of infectious complications and mortality. The primary limitation of the trial is the enrollment of patients with predicted severe acute pancreatitis as nearly two thirds of these patients developed mild acute pancreatitis [104]. There is a clear disconnect with regards to research and clinical practice as enteral nutrition is almost never administered until a patient has 'actual' severe acute pancreatitis. A recent trial randomized patients with 'actual' moderate-to-severe acute pancreatitis, based on the revised Atlanta classification, to early (when a patient reported feeling hungry) versus conventional (once symptoms and laboratory parameters improved) oral refeeding. Other than a shorter length of hospital stay in the early oral refeeding group, there were no differences between the two groups with regards to adverse events or complications [105]. Instead of administering enteral nutrition to all patients with predicted severe acute pancreatitis, a more rational approach would be to define which patients are at risk of developing gut barrier dysfunction and administering enteral or oral nutrition accordingly.

Antibiotics

It is important to differentiate between the use of antibiotics to prevent secondary infection of necrosis versus antibiotics given for the treatment of a suspected or confirmed extrapancreatic infection. The evidence surrounding the use of antibiotic prophylaxis is limited. A recent meta-analysis of 14 RCTs of 841 patients with severe acute pancreatitis found no reduction in infected necrosis, extrapancreatic infections, mortality or surgical intervention by using prophylactic antibiotics [106]. These RCTs have had multiple limitations, and interestingly, another study showed an inverse association between study quality and the absolute risk reduction for mortality in trials of antibiotic prophylaxis [107].

Since SIRS is ubiquitous in acute pancreatitis and differentiating SIRS due to acute pancreatitis versus an extrapancreatic infection (e.g., bacteremia or pneumonia) is not possible, antibiotics are commonly administered. It is rational to obtain blood and urine cultures as well as chest radiographs, begin an antibiotic, and then continue or discontinue antibiotics based on the results. Extrapancreatic infections occur in 24% of patients with acute pancreatitis and, compared to infected necrosis, are diagnosed at a median of 8 versus 26 days after admission, respectively, and rates of bacteremia were significantly higher in those with infected necrosis than other patients with acute pancreatitis [6]. This suggests that treating extrapancreatic infections aggressively with antibiotics early in the course of hospitalization may prevent 'seeding' and secondary infection of pancreatic necrosis [11]. The variability in the documentation and treatment of extrapancreatic infections may be one potential explanation for why prior RCTs of antibiotic prophylaxis reached different conclusions regarding their efficacy in patients with necrotizing pancreatitis. The timing of antibiotic administration may also be important as pancreatic tissue concentrations of antibiotics can be variable in the course of acute pancreatitis based on one experimental study where imipenem tissue concentrations were shown to be high early in the course of acute necrotizing pancreatitis, when there is edema and reduced pancreatic capillary blood flow, but decrease as the edema and blood flow improve but the exact opposite was noted for cefotaxime [108].

Protease inhibitors

While early observational studies and small clinical trials suggested that intravenous PIs may improve outcomes in patients with severe acute pancreatitis [109–112], multiple larger RCTs and a recent meta-analysis, which included 17 trials evaluating the efficacy of intravenous PI in severe acute pancreatitis [113], failed to show improvement in mortality. To date, only one RCT has shown that continuous regional arterial infusion (CRAI) of the PI, nafamostat mesylate, and an antibiotic, imipenem, for 5 days reduced mortality and the need for intervention in severe acute pancreatitis [112]. While this was a positive study, it is by no means definitive and many important questions remain. First, do PIs truly have a beneficial effect or were these favorable results due to an imbalance between the two study arms? Second, how much influence did the use of an antibiotic have on outcomes? Third, if CRAI is truly effective in treating severe acute pancreatitis, what is the ideal timing, dosing, and duration of therapy? Finally, given the invasive nature of CRAI, what are the practical limitations and complications of this intervention? These are questions that will need to be answered in order for this therapy to be more widely utilized.

Expert commentary

Despite decreasing overall mortality, the incidence of acute pancreatitis continues to increase globally and the morbidity as well as mortality remains unacceptably high in patients with severe acute pancreatitis.

There has clearly been progress in two areas of acute pancreatitis. The first is in the primary and secondary prevention of acute pancreatitis. Primary prevention at the present time is limited to prevention of PEP. The use of rectal NSAIDs and/or pancreatic stents in high-risk patients undergoing ERCP has significantly reduced the risk of PEP and severe PEP. However, it should be noted that incidence of PEP was 16.9 versus 9.2% in the placebo and rectal indomethacin arms, respectively, of the landmark trial

by Elmunzer *et al.* [38]. Based on this and an overall PEP incidence of 9.7% in the placebo or no stent arms of a systematic review of 108 RCTs [35], it could be argued that rectal indomethacin is effectively reducing the incidence of PEP in the high-risk patient to the level of an average-risk patient. The largely unanswered questions are whether we will be able to further reduce the incidence of PEP using pharmacological prophylaxis and if pancreatic stents can be replaced by one or more pharmacologic agent(s). While cholecystectomy and alcohol abstinence counseling have been utilized for effectively preventing additional episodes of biliary and alcoholic acute pancreatitis, respectively, our knowledge of additional risk factors for acute pancreatitis, most notably smoking and genetics, continues to expand. This will allow for additional approaches to secondary prevention. The second is in the management of patients with severe acute pancreatitis. This is likely due to a number of factors, including the recognition that patients with persistent SIRS and organ failure are best served in ICUs earlier in the course of their presentation where close observation and monitoring may help improve outcomes. The other factors include the administration of enteral nutrition to maintain the gut barrier and prevent bacterial translocation; antibiotics for extrapancreatic infections that also may prevent 'seeding' of necrosis; and delayed intervention for suspected or confirmed infected pancreatic necrosis using percutaneous drainage in order to allow collections to organize and become amenable to 'step-up' minimally invasive endoscopic and/or surgical drainage as needed. However, it should be emphasized that all of these interventions are focused on complicated or severe acute pancreatitis.

Supportive medical care consisting of fluid therapy, nutrition, and antibiotics continues to be the cornerstone of medical therapy in acute pancreatitis as there are no pharmacologic therapies at the present time that effectively arrest the inflammatory process of acute pancreatitis before the development of complications or severe acute pancreatitis. There have been many RCTs of anti-secretory agents, PIs, immunomodulators, antioxidants and anti-inflammatory agents. These RCTs had a myriad of limitations, including variable timing of drug administration, small patient sample sizes leading to underpowered studies, use of prognostic scoring systems that poorly predict the development of severe acute pancreatitis, inclusion of various subgroups of patients with acute pancreatitis (both mild and severe acute pancreatitis), and the lack of adjustment for the effect of co-interventions (e.g., intravenous fluid quantities, surgical debridement and enteral nutrition). Regardless of study design limitations, the fundamental problem with prior pharmacologic agents is that none of them address the central events that lead to the inflammatory cascade. The most promising agents in this regard focus on the role of calcium signaling in the acinar cell.

Five-year view

We believe that RCTs evaluating pharmacologic agents that target aspects of intracellular calcium signaling will begin enrolling patients. This will occur after these agents undergo dose response and safety studies. As there are no reliable methods of predicting severe acute pancreatitis at the present time, these initial RCTs will likely enroll consecutive patients presenting with acute pancreatitis with clear and meaningful inclusion and exclusion criteria. They will follow either the number of days of SIRS or persistent SIRS as a measure of therapeutic response since persistent organ failure, necrosis, and mortality occur infrequently and will require extremely large sample sizes to demonstrate significant differences between drug and placebo. In addition, persistent SIRS has excellent negative predictive value and is strongly associated with excess resource utilization. Regulatory agencies, such as the FDA, will need to determine if SIRS is an acceptable end point for these RCTs. There will be efforts to develop an acute pancreatitis activity index; however, this will likely only be superior to the aforementioned outcomes if it incorporates patient-reported outcomes and is validated in a large prospective study. There will be progress in reducing the costs associated with caring for patients with acute pancreatitis by potentially discharging patients with mild acute pancreatitis for home care, using abdominal imaging more prudently, and preventing readmissions within 30 days. A combination of pharmacologic agents will likely be shown to be more effective than pancreatic stents for preventing PEP in high-risk patients and will also be shown to be far less costly, prompting their use in all patients undergoing ERCP. The optimal timing of cholecystectomy will be clarified by the PONCHO trial. The genetic and epigenetic contributions that increase the risk of alcohol and smoking-related acute pancreatitis will be further elucidated and may be used for risk stratification and counseling. There will be progress in supportive care measures as well. While a fluid therapy RCT will not be possible without a publicly funded large multi-center consortium (since industry is unlikely to support a trial of an extremely low cost intervention), pilot studies of agents that block vascular leak in patients who present with risk factors for increased fluid sequestration will need to be explored. Enteral nutritional support will be focused on patients at risk of developing gut barrier dysfunction since it is largely these patients who are at risk of infectious complications. Given the increasing data supporting the use of the oral route for nutrition, even in patients with severe acute pancreatitis, there will be efforts made to identify which patients need a nasoenteric feeding tube versus those who can directly start on an oral diet. Serum markers that accurately differentiate the SIRS of acute pancreatitis versus sepsis due to extrapancreatic infections may allow us to develop a more pragmatic approach to the use and choice of antibiotics.

Financial & competing interests disclosure

V.K. Singh is a consultant to Novo Nordisk, D-Pharm, Interscope, Boston Scientific and AbbVie. V.K. Singh is also on the advisory board for Enteromedics and Salix and receives travel support from Cook Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

doi: 10.1586/17474124.2015.1048225

Key issues

- Prior trials of pharmacologic agents have not shown a treatment benefit in acute pancreatitis because either their mechanism of action lies too far 'downstream' of the initial intracellular events and/or clinical trial design problems.
- Well-designed trials of pharmacologic agents that target calcium signaling within acinar cells represent the clearest prospect for an effective therapy.
- Primary prevention of acute pancreatitis is largely focused on preventing post-ERCP pancreatitis in high-risk patients using rectal NSAIDs and/or pancreatic stents but there are multiple trials currently underway to determine if combinations of pharmacologic agents could potentially replace the use of prophylactic pancreatic stents.
- Secondary prevention focuses on cholecystectomy for acute biliary pancreatitis and counseling on alcohol and smoking abstinence.
- There will be substantial cost savings to the healthcare system if new paradigms of care are considered for the care of the mild acute pancreatitis, if less imaging is pursued and 30-day readmission rates are reduced.
- Studies that have evaluated fluid therapy are hampered by 'reverse causation' bias. Future approaches to fluid therapy will need to focus on aggressive hydration of patients at risk of fluid sequestration in combination with agents that address capillary leak.
- Instead of administering enteral nutrition to any patient with predicted severe acute pancreatitis, future efforts will focus on determining which patients are at risk for gut barrier dysfunction and which will require nasoenteral versus oral nutritional support.
- Methods will need to be developed to differentiate the systemic inflammatory response syndrome of acute pancreatitis from that of extrapancreatic infections that occur in up to 25% of patients. This will allow for a more tailored approach to the use and choice of antibiotics.

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