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Conservative Therapy of Acute Pancreatitis: Volume Substitution and Enteral and Parenteral Nutrition

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Introduction

Acute pancreatitis is an often devastating inflammatory condition of the pancreas that leads to extensive worldwide morbidity and mortality [1]. In fact, in the United States, acute pancreatitis is among the most common reasons for patients to be hospitalized for a digestive illness [2]. The substantial human costs of this disease, with billions in annual healthcare dollars spent worldwide, has led to extensive efforts to establish a pharmacologic treatment for this disease. Unfortunately, as of 2022, there is no specific medical therapy that specially targets acute pancreatitis or that has been useful to improve important clinical outcomes.

Over the past 50 years, extensive efforts have been made to develop targeted pharmaceutical therapies, but none have demonstrated benefit in randomized controlled trials. Agents directed at reducing pancreatic secretions, including histamine-2 blockers, such as cimetidine, glucagon, atropine, somatostatin and its analogue octreotide, do not reliably affect morbidity or mortality [3–5]. Antiprotease therapy with aprotinin and gabexate mesilate are equally ineffective, as is therapy with lexipafant, a platelet-activating factor antagonist [6,7].

Recently, as discussed elsewhere in this textbook, rectal nonsteroidal anti-inflammatory drugs (NSAID) have been demonstrated to be helpful in reducing the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis due to regulation of proinflammatory mediators. Rectal NSAID function by inhibiting phospholipase A2 activity, including arachidonic acid products and platelet-activating factors [8,9]. One NSAID in particular, rectal indomethacin, has been used extensively since 2012 following the publication of a randomized, placebo-controlled trial in patients undergoing ERCP considered to be at high risk for pancreatitis [9]. The trial found that a single 100 mg dose of rectal indomethacin significantly reduced the risk of pancreatitis from 16.9% in those receiving placebo to 9.2% in those receiving indomethacin.

However, with the exception of rectal indomethacin, there are currently no specific pharmacologic therapies advocated for the treatment of acute pancreatitis [10]. Supportive measures, including the use of fluid resuscitation, nutrition, and aggressive intensive care unit care, have become the cornerstone of conservative therapies in treating this disease.

This chapter focuses specifically on the conservative therapies of fluid resuscitation and enteral and parenteral nutrition. It will review the importance of the pancreatic microcirculation and its effects on the pathogenesis and prognosis of acute pancreatitis. It will discuss animal and human clinical trials that have evaluated the role of different types, volumes, and rates of fluid resuscitation. Finally, current recommendations in regard to administering fluids in acute pancreatitis will be provided. The latter aspect of the chapter will focus specifically on the role of enteral and parenteral nutrition in the treatment of acute pancreatitis, with a review of clinical trials and important recommendations for nutritional care on patients with this disease.

Fluid Resuscitation

The Pancreatic Microcirculation and Acute Pancreatitis

It is critically important to understand the intricacies of the pancreatic microcirculation when discussing the role of fluid resuscitation in acute pancreatitis. The arterial supply to the pancreas is derived from the two main proximal trunks of the aorta: the celiac trunk and superior

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mesenteric artery. The splenic and common hepatic arteries (as well as the left gastric artery, which does not supply the pancreas) arise from the celiac trunk. The splenic artery gives rise to the penetrating branches of the body and tail of the pancreas, while the common hepatic artery, via its branch the gastroduodenal artery, supplies the pancreatic head through the anterior and posterior superior pancreaticoduodenal arteries. The anterior and posterior inferior pancreaticoduodenal arteries, arising from the superior mesenteric artery, supply the head and neck of the pancreas, and form vascular anastomoses with the superior pancreaticoduodenal arteries. This vascular network features extensive collateralization, thus ensuring adequate pancreatic tissue perfusion.

From these large arteries arise the intralobular arteries, which run within the pancreas often parallel to the pancreatic ducts. The intralobular arteries give rise to the pancreatic microcirculation, a vast network of capillaries and venules that supply the pancreatic acinus with a rich blood supply [11]. An exocrine lobular plexus with multiple fine capillaries represents the basic vascular unit within the pancreas, and flow from the vascular plexus is almost 20 times more likely to prefer the pancreatic islet cells than the acinus. As a result, the pancreatic acinus is extremely prone to low vascular flow states when there is lack of circulating blood flow to the pancreas [12]. This susceptibility is why the pancreatic acinus can be so prone to damage with even a slight perturbation in systemic blood flow.

Disturbance to the blood flow within the pancreatic microcirculation due to acute pancreatitis can occur for several reasons: hypovolemia, increasing capillary permeability, and hypercoagulability causing microthrombi, among others [13–16]. The generation of oxidative free radicals with subsequent capillary endothelial damage has also been implicated. This alteration in microcirculation significantly increases the degree of pancreatic ischemia, irrespective of etiology, thus exacerbating the systemic inflammatory response syndrome (SIRS) and potentially leading to multisystem organ failure.

Once significant acinar blood flow has been disturbed, acinar cell injury occurs. Acinar cell injury then causes the release of multiple proinflammatory cytokines and vasoactive mediators, including tumor necrosis factor α, histamine, bradykinin, interleukin 1 (IL-1), IL-2, IL-6, platelet-activating factor, and endothelin-1, which are recruited to the pancreatic microcirculation and delivered to the acinar cells [17–19]. Once this proinflammatory cascade is set into motion, the systematic sequelae of acute pancreatitis, including the collapse of the systemic circulation leading to multisystem organ failure, can occur. Once initiated, this process is exceedingly difficult to reverse.

The role of aggressive fluid resuscitation is essentially to try to perfuse the acinar tissue sufficiently in the face of such overwhelming antagonism of the normal physiologic maintenance of adequate tissue perfusion pressure. Although fluid resuscitation by itself does not have an effect on the proinflammatory mediators leading to circulatory collapse, the sequelae of maintaining adequate tissue perfusion may seek to slow or ameliorate at least part of the inflammatory cascade. The hope for intravenous fluid resuscitation in acute pancreatitis is that adequate tissue perfusion will perfuse the pancreatic microcirculation so that pancreatic necrosis and its subsequent complications can be minimized or even prevented.

Animal Studies

There have been extensive animal studies in the pathophysiology and treatment of acute pancreatitis, specifically in regard to establishing a definitive pharmacologic therapy for blunting the proinflammatory content of this disease. However, despite the important role of fluid resuscitation in acute pancreatitis, relatively few animal studies have been exclusively devoted to this subject. The critical question asked by animal studies in acute pancreatitis are the same as in human studies: How much fluid should be given? What type of fluid should be given? Is colloid or crystalloid fluid a better choice? What are the complications of using overly aggressive fluid resuscitation?

Two animal studies have demonstrated the importance of aggressive fluid resuscitation, irrespective of the type of fluid utilized. Juvonen et al., using a pig model of Na-taurocholate-induced pancreatitis, showed that the signs of splanchnic hypoperfusion can be prevented with fluid resuscitation [20]. The investigators found that the PCO_2 gap increased and portal venous blood flow decreased in pigs with acute pancreatitis, but did improve significantly with resuscitation. Niederau et al. have also demonstrated in a choline-deficient, ethionine-supplemented diet mouse model that hydration by subcutaneous fluid markedly improved survival and normalized the hematocrit without having significant biochemical or morphologic effects [21].

Crystalloid resuscitation has been studied only sparingly in animal studies of acute pancreatitis. Knol et al. evaluated the effect of low and high infusion rates of lactated Ringer's solution in 14 dogs with bile trypsin pancreatitis [22]. They found that pancreatic blood flow decreased to a greater extent in the low infusion group compared to the high infusion group. Crystalloid resuscitation with a balanced salt solution adequately restored plasma volume, supported tissue perfusion and prevented excessive hemodilution without detrimental effects on pulmonary pressures or oxygenation in a canine model of acute hemorrhagic pancreatitis [23].

The majority of animal studies dealing with fluid resuscitation have used colloid solutions, most notably dextran, and generally found improved outcomes compared with crystalloid resuscitation. One suspected reason for improved outcomes with colloids has been that they are not as permeable to leakage in the pancreatic microcirculation compared with crystalloids. By remaining in the luminal environment, circulatory blood flow is better maintained, and inflammatory mediators are less able to access the acinus [24–28].

Thus, in summary, animal studies have been relatively sparse, and the majority of these have been completed with colloid rather than crystalloid solutions. However, these studies have not been able to answer effectively the questions of which solution is most appropriate, what is the optimal rate of fluid resuscitation, and what are the consequences of overly aggressive resuscitation. Surprisingly, as detailed below, the clinical studies in humans have not appreciably answered these questions satisfactorily either.

Human Studies

Despite the universally accepted paradigm that aggressive fluid resuscitation is an important element of supportive care in acute pancreatitis that leads to improvements in important clinical outcomes, few studies and even fewer randomized controlled trials have been performed on this treatment. Questions about the rate of resuscitation, type of fluids, and consequences of over-aggressive resuscitation remain unanswered. However, in the last decade more attention had been focused on this important clinical area, and several randomized trials are planned to try to answer these critically important questions.

The original investigation in humans about the importance of aggressive fluid resuscitation was carried out by Baillargeon, Banks, and colleagues in the 1990s. They emphasized the importance of resuscitation in improving clinical outcomes. In a retrospective cohort study, they found that hemoconcentration with an admission hematocrit >47% or failure of admission hematocrit to decrease at approximately 24 hours were strong risk factors for the development of pancreatic necrosis [29]. Multiple subsequent studies have validated these findings, including the Banks group who performed a retrospective study to determine whether fluid resuscitation could prevent pancreatic necrosis among patients with hemoconcentration at the time of admission [30–35].

As these data suggest, inadequate fluid resuscitation leading to poor pancreatic microcirculatory perfusion has been associated with acute necrotizing pancreatitis [33]. Specifically, we now know that early fluid resuscitation has more of a therapeutic effect than delayed fluid resuscitation. Although early fluid resuscitation is generally agreed upon as an intervention of paramount importance, there are currently no standard guidelines on the optimal fluid type, volume, rate, or duration of treatment. Despite the lack of standard guidelines, studies on the rate and volume of fluid therapy suggest early aggressive fluid resuscitation results in the best outcomes. When compared to early nonaggressive (<500 mL) fluid resuscitation, early moderate (500–1000 mL) to aggressive (>1000 mL) fluid volume administration significantly reduces the need for invasive interventions, with some evidence suggesting a trend towards lower complications with early moderate to aggressive fluid resuscitation [36]. Although human studies on the rate of hydration consistently show decreased morbidity and mortality with aggressive hydration in the first 24 hours, the total volume of hydration at the 48-hour mark seems to have a limited effect on patient outcomes [36,37].

The current American College of Gastroenterology (ACG) guidelines recommend 250–500 mL/h of isotonic crystalloid solution in the first 12–24 hours, with frequent re-evaluation every 6 hours and an ultimate goal of decreasing the blood urea nitrogen (BUN) levels [38]. Some experts recommend that in addition to the 1–2 L fluid bolus given in the emergency department, the starting infusion should be at a rate of 250–300 mL/h or enough to produce a urine output of at least 0.5 mL/kg per hour [39]. The goal within the first 24 hours is a total infusion volume of 2.5–4 L, with adjustments to be made based on the patient's age, weight, physical exam, and comorbid conditions [40]. Similarly, the current American Gastroenterological Association Institute (AGA) guidelines advise using goal-directed therapy for fluid management but note to proceed judiciously so as to avoid potential complications from overly aggressive fluid resuscitation [41].

The type of resuscitation fluid has been minimally studied. However, in a widely cited manuscript, Wu et al. found that the use of lactated Ringer's solution, in place of normal saline, resulted in less SIRS and a decreased C-reactive protein at 48 hours [42]. However, the small sample size of 40 patients limits the study. Nevertheless, more recent randomized controlled trials substantiate these results. De-Madaria et al. compared lactated Ringer's solution to normal saline solution and found that lactated Ringer's led to less SIRS criteria and lower C-reactive protein levels than normal saline. *In vitro*, they also observed that lactated Ringer's inhibited both the activation of macrophages to their inflammatory phenotype and the activity of NF-κB, a transcription factor involved in inflammation, while normal saline and Ringer's solution without lactate did not inhibit such processes [43]. In another randomized controlled trial, Choosakul et al. revealed that lactated Ringer's solution significantly decreased SIRS compared to normal saline 24 hours after the development of acute pancreatitis but did not show any significant differences in SIRS at 48 hours [44].

A meta-analysis conducted by Iqbal et al. confirmed these findings by demonstrating that lactated Ringer's solution resulted in lower rates of SIRS development compared to normal saline at 24 hours [45]. However, a randomized controlled trial conducted by Lee et al. found no significant difference in SIRS between normal saline and lactated Ringer's, but did reveal that lactated Ringer's resulted in a shorter length of stay and fewer ICU admissions than normal saline [46]. In patients undergoing ERCP, aggressive fluid resuscitation using lactated Ringer's solution has been demonstrated to be an effective deterrent for the development of post-ERCP pancreatitis [47]. Thus, although these patients are not in the same exact clinical scenario as patients not undergoing ERCP, these results do suggest that the use of lactated Ringer's solution has a beneficial effect.

The issue of over-aggressive hydration and risk of poor outcomes, particularly the development of abdominal compartment syndrome, has been highlighted by two studies. The first, a retrospective evaluation of 99 patients with severe acute pancreatitis in Sweden, determined that patients receiving 4000 mL or more of fluids during the first 24 hours ($n = 32$) developed more respiratory complications (66% vs. 53%; $P = 0.001$) than patients who received less than 4000 mL of fluid [48]. Mao et al. have also reported improved survival rates by controlling the amount of fluid resuscitation within the first 72 hours in 83 patients with severe pancreatitis [49]. In addition, in a randomized controlled trial of patients with predicted severe pancreatitis whose hematocrit was aggressively lowered upon admission, those with aggressive lowering of their hematocrit had greater morbidity and mortality [50]. A subsequent meta-analysis of aggressive vs. nonaggressive fluid therapy determined that although no statistically significant difference in mortality existed between the two groups, patients receiving aggressive fluid resuscitation possessed a higher risk for acute kidney injury, as well as acute respiratory distress syndrome [51].

Thus, although important inroads have been made into the role of aggressive fluid resuscitation in the critical issue of supporting the pancreatic microcirculation in acute pancreatitis, several questions remain—particularly how best to monitor the rate of resuscitation and at what point the critical juncture of over-resuscitation occurs. Lactated Ringer's solution appears to represent an important breakthrough in the type of crystalloid solution to be used in this regard but further randomized controlled trials stratifying by the type of crystalloid solution are necessary. Continued animal studies into the effects of crystalloid and colloid solutions on the pancreatic microcirculations are in order, as well as carefully designed human clinical trials using varying fluid solutions and rates with an emphasis on patient monitoring and safety (Table 24.1).

Table 24.1 Important human studies of fluid resuscitation in acute pancreatitis.

Study type	Number of patients	Comparison group	Outcome
Retrospective [29]	65	Aggressive (Hct <47) vs. nonaggressive	Hct >47 developed necrosis
Retrospective [48]	99	Aggressive (4 L) vs. nonaggressive	Aggressive with more respiratory complications and increased ICU care
Retrospective [34]	45	Early vs. late resuscitation	Increased mortality in late
Retrospective [35]	434	Early vs. late resuscitation	Less SIRS, organ failure, ICU admissions, LOS in early
RCT [47]	62	Aggressive (3 mL/kg per h) vs. nonaggressive using LR in ERCP	Less hyperamylasemia and abdominal pain in aggressive group
RCT [50]	115	Aggressive (<35 Hct in first 24 h) vs. nonaggressive	A higher incidence of sepsis and decreased survival in aggressive group
RCT [42]	40	LR vs. normal saline	LR had decreased SIRS and CRP at 24 hours
RCT [43]	40	LR vs. normal saline	LR led to decreased SIRS and CRP than normal saline
RCT [44]	47	LR vs. normal saline	LR significantly decreased SIRS at 24 hours compared to normal saline, but had no significant difference at 48 hours
RCT [46]	121	LR vs. normal saline	LR resulted in decreased LOS and ICU admissions but led to no significant difference in SIRS compared to normal saline

Hct, hematocrit; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; LOS, length of stay; LR, lactated Ringer's solution; CRP, C-reactive protein.

Enteral and Parenteral Nutrition

Nutritional supplementation has long been an important component of conservative treatment in acute pancreatitis. Since most patients with acute pancreatitis must be "nothing by mouth" for at least part of their hospitalization, the mechanism of nutritional supplementation and type has been an active area of clinical research for many decades. Although the standard of care for many years included nothing per mouth and "resting" the pancreas by limiting enteral intake, recent studies have proved that early enteral feeding appears to be of significant benefit to clinical outcomes.

The disadvantage of maintaining patients nothing by mouth is that bowel rest is associated with intestinal mucosal atrophy and increased infectious complications due to bacterial translocation [52]. In order to maintain gut barrier function, therefore, enteral feeding is preferred over parenteral feeding in the management of acute pancreatitis. This preference has been proven in multiple randomized controlled trials dating back to the early 1990s, and meta-analyses have consistently demonstrated the importance of enteral versus parenteral nutrition in both interstitial and predicted severe acute pancreatitis [53–57]. Currently there is no rationale to use parenteral over enteral nutrition in the setting of acute pancreatitis. Even in patients who cannot tolerate a full enteral diet, at least some degree of enteral nutrition should be provided to maintain gut barrier function. Early enteral nutrition (within 48 hours) after admission has been found to reduce mortality, multiple organ failure, operative interventions, and infections when compared to late enteral nutrition and parenteral feeding [58,59]. Current AGA guidelines corroborate these findings, as the AGA advising panel strongly recommends early (within 24 hours) oral feeding and, in patients who cannot feed orally, enteral rather than parenteral nutrition to generate the best outcomes [41].

In mild acute pancreatitis, early initiation of oral intake with a low-fat soft solid diet is often tolerated and has been demonstrated to be just as efficacious as tube feeding [60]. Further study has also demonstrated that even in patients with predicted severe acute pancreatitis, early oral vs. on-demand tube feeding has demonstrated equivalent efficacy in a randomized controlled trial [61]. Enteral feeding is recommended within 3 days of hospitalization, typically after cessation of nausea, vomiting, discontinuation of parenteral analgesics, reduction in abdominal pain, and return of bowel sounds. However, one study suggests that early oral refeeding based on hunger rather than on clinical and laboratory measures proves effective for introducing nutrition earlier to patients with acute pancreatitis without more complications than conventional refeeding based on clinical parameters, and it reduces length of stay compared to conventional refeeding [62]. Moreover, feeding can be started with a low-fat solid diet and does not need to be initiated using the archaic clear liquid, mechanical soft, and low-fat method [63]. Moraes et al. found in a randomized controlled trial that patients who received a full solid diet as opposed to either a clear liquid diet or a soft diet and who had no abdominal pain relapse had the shortest length of stay (median 1.5 days shorter). However, when considering patients who had abdominal pain relapse, the length of stay was similar among the three groups, and the authors found no difference in pain relapse between the three different diets [64].

The choice between nasojejunal or nasogastric feeding has been debated for quite some time with nasojejunal feeding being favored—again because of the issue of achieving pancreatic rest. However, recent studies have suggested that nasogastric feeding may be just as efficacious and well tolerated as nasojejunal feeding when evaluated in a randomized controlled setting and demonstrate benefits when compared to nil per os [65,66]. Because of no apparent mortality benefit of one over the other, the AGA guidelines recommend either nasogastric or nasojejunal feeding [41].

The issue of type of feeding has been inadequately studied, but there has been a meta-analysis evaluating 20 randomized controlled trials comparing different formulations [67]. The authors concluded that the use of polymeric, rather than (semi)elemental, formulation does not lead to a significantly higher risk of feeding intolerance, infectious complications, or death in patients with acute pancreatitis. Neither the supplementation of enteral nutrition with probiotics nor the use of immunonutrition significantly improved the clinical outcomes. A Cochrane Database review also found similar low-quality evidence differentiating the types of formulations and their benefit in acute pancreatitis [68]. In addition, a recent study of the use of probiotics in acute pancreatitis demonstrated worsening mortality due to bowel ischemia in the group receiving probiotics, and it is thus advised that probiotics should not be used in patients with acute pancreatitis [69].

Thus, in summary, enteral feeding is favored over parenteral feeding in acute pancreatitis based on improvement in important clinical outcomes. Oral feeding should be initiated within 72 hours of admission in all patients using a low-fat diet. If patients cannot tolerate oral feeding, nasoenteric feeding, usually with a nasogastric feeding tube, can be employed. In those patients in whom appropriate enteral feeding is not tolerated, low-level "trickle" feeding should be used to help prevent gut translocation of bacteria, which can lead to infected necrosis. Patients should not be given probiotics, as these formulations have demonstrated an increased risk of mortality due to mesenteric ischemia.

Conclusions

Supportive care in acute pancreatitis is critical to achieving optimal patient outcomes in the context of no targeted pharmacologic options in this disease. Aggressive fluid resuscitation and the initiation of early enteral feedings have revolutionized the care of patients with acute pancreatitis. Further studies—specifically targeting the type of fluids and enteral nutrition formulations in randomized controlled trial format—are needed, however, in order to optimize further conservative care for these patients.

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