Review article

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VOLUME THERAPY IN ACUTE PANCREATITIS

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Fundamental management is required soon after a diagnosis of acute pancreatitis has been made and includes monitoring of the conscious state, the respiratory and cardiovascular system, the urinary output, adequate fluid replacement and pain control, blood purification therapy and nutritional support. An adequate dose of fluid replacement is essential to stabilize cardiovascular dynamics and the dose should be adjusted while assessing circulatory dynamics constantly. Current clinical practice guidelines recommend aggressive fluid resuscitation despite limited prospective data. Fluid therapy remains the mainstay of early management of patients with acute pancreatitis and severe acute pancreatitis. High-level evidence is lacking to guide protocols for fluid resuscitation in patients presenting with acute pancreatitis. In those patients with severe acute pancreatitis, the available evidence indicates that controlled fluid resuscitation with crystalloids and colloids offers the best outcome. Hematocrit remains a useful marker to guide fluid resuscitation in acute pancreatitis. However, the timing and ideal "cut-off" level needs to be determined. *Acta Medica Medianae 2013;52(3):55-60.*

Key words: *acute pancreatitis, guidelines, resuscitation*

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Introduction

Acute pancreatitis is potentially a fatal disease and its mortality rate is 2.1–7.8%. In 10–20% of patients with acute pancreatitis, the disease becomes severe and the mortality rate associated with acute pancreatitis increases up to 14–25% if the disease is aggravated (1). The prognosis of acute pancreatitis is determined by two factors including organ failure and pancreatic necrosis.

Patients with a diagnosis of acute pancreatitis should be hospitalized. Initial treatment should be started as soon as possible. Adequate respiratory and cardiovascular monitoring is crucial involving the conscious state, temperature, pulse rate, blood pressure, urinary output, respiratory frequency, and oxygen saturation. Initial treatment and adequate monitoring should be continued while patients are being transferred from the emergency room to a sick ward and from a clinic to a general hospital. Initial treatment includes fasting, adequate dose of fluid replacement and sufficient pain relief.

Along with the etiologic diagnosis of acute pancreatitis, severity assessment of acute pancreatitis should be conducted based on the severity scoring system of acute pancreatitis of the Japanese Ministry of Health, Labour, and Welfare (2008).

Acute pancreatitis can become severe even if it is mild at the initial visit of a patient, so repeated severity assessment is crucial. Strict respiratory and cardiovascular management is required in patients with a diagnosis of severe acute pancreatitis, so transference to a medical facility should be considered where intensive care, interventional treatment, blood purification therapy and nutritional support are available. Prophylactic antibiotic administration is recommended for severe acute pancreatitis. There is no consensus on the usefulness of protease inhibitors. Enteral nutrition initiated in the early phase of the disease is superior to intravenous hyperalimentation.

What are the parameters for adequate dose of fluid replacement as the initial treatment of acute pancreatitis?

Initial fluid replacement should be performed to secure, as its target, stable cardiovascular dynamics with an average blood pressure of more than 65 mmHg as their parameters and the urinary output of 0.5–1 ml/kg/h.

In acute pancreatitis, increased vascular permeability and decreased colloid osmotic pressure give rise to a leakage of extracellular fluid into the peripancreas, the retroperitoneum as well as into the abdominal and thoracic cavities, which results in a loss of a large volume of the circulating plasma. Acute cardiovascular disorders brought

about in this manner are one of the causes of aggravated initial condition of acute pancreatitis. Therefore, it is mandatory to stabilize the cardiovascular dynamics mainly through replacing a sufficient dose of extracellular fluid initiated in the early phase of the disease. Calcium and potassium chloride should be replaced if deficiencies arise. Hyperglycemia is managed with insulin as needed.

In patients with severe acute pancreatitis, continuous monitoring of central venous pressure or pulmonary wedge pressure, blood gas analysis, and electrolyte measurement is crucial to determining the adequate volume that must be replaced. Oxygen is administered as needed to maintain at least 95% of oxygen saturation. A recent report has shown that excessive fluid replacement that has been conducted rapidly and continuously for a long time despite the presence of acute pancreatitis has adverse effects on the prognosis (2). When the initial treatment is delivered, repeated assessment of the cardiovascular dynamics should be conducted. Immediately after the start of treatment in particular, the assessment should be conducted every 4–6h and the transfusion speed should be adjusted so that an adequate dose of fluid can be achieved.

Given the lack of an effective pharmacologic treatment, attention has focused on optimizing supportive measures. In particular, data from experimental animal models of acute pancreatitis suggest that vigorous fluid resuscitation may enhance the pancreatic microcirculation (3). The notion that more aggressive fluid resuscitation could potentially prevent necrosis was further advanced by indirect evidence from a small retrospective study that indicated nearly all patients with hemoconcentration on admission (hematocrit >44%) who did not experience a decrease in hematocrit during the first 24h of hospitalization went on to develop pancreatic necrosis. On the basis of this limited evidence, nearly all current clinical practice guidelines recommend vigorous fluid resuscitation for initial treatment of acute pancreatitis. In issue of the American Journal of Gastroenterology, Enrique de-Madaria et al. present findings from a prospective observational cohort study designed to evaluate the impact of early fluid resuscitation on clinical outcomes in patients with acute pancreatitis (4).

Early fluid resuscitation was defined as the volume of fluid administered during the initial 24h of hospitalization. The study investigators classified resuscitation volumes according to quartiles as low (lowest quartile), moderate (second and third quartile), and high (highest quartile). Specific outcomes measured included persistent organ failure (>48h, primary outcome) and local complications as well as mortality as secondary end points.

The study presents several interesting findings. First, the majority of patients received between 3 and 5l of fluid during the initial 24 h of hospitalization. Next, at least according to the current treatment recommendations, patients in the lowest quartile of fluid resuscitation (<3.1l) may have been arguably under-resuscitated. Nevertheless, there was no excess in local complications, organ failure, or mortality among this group of patients. By contrast, patients who received the highest volumes of fluid (>4.1l) experienced a significant increase in the rate of persistent organ failure and local fluid collections. This association persisted after adjusting for several potential confounders including age, Charlson comorbidity score, body mass index, and systemic inflammatory response syndrome status.

Each patient's actual fluid resuscitation parameters were based on clinician judgment, which complicates the interpretation of the study findings. In particular, although increased fluid resuscitation was associated with numerous complications, it is not possible to infer causation based on the present study design. The reverse may be true such that patients with more severe illness would receive greater fluid resuscitation by their treating physician.

The present findings call into question several long held beliefs regarding fluid resuscitation in acute pancreatitis. First, it appears clear that not all patients require or benefit from "aggressive" fluid resuscitation. Second, there did not appear to be a benefit to administration of large volume resuscitation (>4l) during the first 24h of hospitalization. This latter finding is consistent with a recent randomized-controlled trial conducted in China, in which patients with acute pancreatitis who had evidence of hemoconcentration (hematocrit >44%) at admission were assigned to either an aggressive resuscitation strategy or a more conservative approach (5). In the aggressive resuscitation arm, fluids were administered to achieve a hematocrit of 35% or less within 48h. As expected, patients assigned to the aggressive treatment arm received greater fluids compared with the more conservative treatment group (mean 4.8 vs. 3.8l, respectively, P=0.005). However, patients in the aggressive treatment group experienced greater frequency of sepsis and higher mortality during hospitalization. Similarly, patients who received >4l of fluid during the first 24h of hospitalization were noted to have increased frequency of respiratory complications in a retrospective cohort study from Sweden (6).

Besides the volume of fluid resuscitation, recent attention has also focused on the manner in which fluid resuscitation is delivered. Several recent retrospective studies have suggested that the proportion of fluid administered in the initial phase of acute pancreatitis may be more important than the total aggregate volume (7). In the present study by de-Madaria et al., it would have been helpful to know the rate at which fluids were administered, e.g., as bolus or continuous infusion. It is possible, for example,

that an approach similar to that advocated for septic shock may prove useful in acute pancreatitis. Current recommendations in septic shock are to administer an initial volume challenge to determine whether a patient's condition is fluid responsive rather than providing ongoing high-volume fluid administration at a continuous rate (8).

There is a need to review the data on fluid resuscitation in acute pancreatitis to aid the development of evidence-based guidelines. All available major publications from the past 45 years were considered and a total of 12 studies were identified describing regimens for fluid therapy. These included 2 randomized controlled trials, 1 retrospective cohort study, and 9 reviews.

Rationale for Fluids in Acute Pancreatitis

The impact of retroperitoneal fluid losses and dehydration on the development of hypovolemia seen in patients with severe acute pancreatitis resulting in high mortality was recognized in the 1950s (9). This fluid loss was largely shown to respond to intravenous fluid therapy, the initial understanding was that the shock was mainly due to a loss of red blood cells (10). Thereafter, despite the link between hemoconcentration at admission and mortality in acute pancreatitis being suggested by Davis et al. and Gray et al., a reduction in hematocrit in the first 48 hours was considered a poor risk factor in acute pancreatitis as evidence by the scoring system proposed by Ranson et al. (11-13).

*Table 1.*Summary of the available studies to date on fluid therapy in acute pancreatitis

Author, Year, Type of study (sample size)	Conclusion	Level of evidence
Mao *et al*. (26) 2010 RCT (n=155)	Rapid hemodilution increases incidence of sepsis within 28 days and in-hospital mortality HCT should be maintained between 30% and 40% in acute response stage	I
Mao *et al*. (27) 2009 RCT (n=76)	Controlled fluid resuscitation offers better prognosis in patients with severe volume deficit within 72 h of severe acute pancreatitis onset	I
Gardner *et al*. (20) 2009 Retrospective cohort (n=45)	Patients with severe acute pancreatitis should receive 1/3 or more of initial 72 h cumulative i.v. fluid volume during first 24 h	III
Pezzilli *et al*. (23) 2010 Review	Prompt adequate i.v. fluid administration to correct volume deficit and maintain basal fluid requirements	-
Forsmark *et al*. (19) 2007 Review	Target: urine output 0.5 mL/kg body weight/h or more Crystalloids: preferred Indications for colloids: Packed red blood cells, when HCT falls less than 25% Albumin: serum albumin level drops to 2 g/dL Precautions: evidence of cardiovascular system dysfunction or pulmonary capillary leak syndrome Central venous pressure or pulmonary artery catheter indicated in severe acute pancreatitis	V
Otsuki *et al*. (21) 2006 Review	Ringer's lactate: 60-160 mL/kg body weight/day About 1/3-1/2 of amount required for first 24 h, within the first 6 h Hourly: pulse, blood pressure, urine output, central venous pressure monitoring	V
Pandol *et al*. (22) 2007 Review	Severe volume depletion: 500-1,000 mL/h for several hours with amount of fluid reduced, once signs of severe volume depletion have subsided non pancreatic fluid loss: 300-500 mL/h No clinical volume depletion: 250-300 mL/h Fluid rates reassessed 1-2 hourly in severely depleted patients or at least 4 hourly for other patients	V
Banks *et al*. (18) 2006 Review	Aggressive i.v. fluid replacement Aggressive hydration (e.g. a bolus of fluids to achieve hemodynamic stability, followed by 250-500 mL/h crystalloids in an average sized patient without substantial kidney or heart disease	V
Whitcomb *et al*. (28) 2006 Review	Intravenous hydration 250-300 mL/h or more for 48 h	V
Tenner *et al*. (24) 2004 Review	Aggressive i.v. fluid replacement	V
Vege *et al*. (25) 2004 Review	After initial rapid resuscitation, fluid replacement should aim at 35 mL/kg body weight/day	V
Wilmer *et al*. (29) 2004 Review	Crystalloids: preferred	V

HCT: hematocrit; RCT: randomized controlled trial
*Guidelines/recommendations (American Gastroenterology Association, Italian, Japanese)

Ranson et al. attributed the low hematocrit to pre-existing anemia encountered in alcoholics, while Trapnell found the fall in hematocrit to correlate with internal hemorrhage (14). The early use of fluid therapy has certainly reduced early mortality in acute pancreatitis associated with hypovolemia.

In the 1990s, the importance of hemoconcentration was re-visited by the group from the Brigham and Women's Hospital in Boston (15, 16). Since then, hemoconcentration based on a serum hematocrit level at admission has been consistently demonstrated to be linked to the development of pancreatic necrosis (17). Pancreatic microcirculation depends on circulating volume and responds poorly to other influences.

Available Evidence on Regimens for Fluid Therapy in Acute Pancreatitis

- Human Studies - Table 1 lists the articles/ studies involving fluids in acute pancreatitis, their conclusions, as well as, the level of evidence (18 -30).

- Animal Studies - Animal studies conducted over the last four decades in the context of aiding the decision on the choice of fluid in the clinical setting have not been particularly helpful (31).

Based on the review of literature we can conclude that hemoconcentration in a patient with acute pancreatitis (based on serial measurements of hematocrit) within the first 48 hours of admission is a marker of poor prognosis and indicates the need for fluid resuscitation. The ideal cut-off level for serum hematocrit (44% or 47%) remains to be determined. What can also be concluded from the available literature is that fluid therapy remains the cornerstone in the early management of acute pancreatitis and especially in the prevention of severe acute pancreatitis. In patients who go on to develop severe acute pancreatitis either due to a late presentation or despite resuscitation, fluid therapy has the potential to reduce the progression of pancreatic necrosis and its associated risk of mortality.

In 2008, Gardner et al. reviewed the available evidence on fluid resuscitation in acute pancreatitis and found that there was a paucity of evidence to support clinical recommendations at that time (32). To date, there continues to be a lack of high-level evidence to guide the ideal "initial" fluid strategy for all patients presenting with acute pancreatitis in terms of choice of fluid, namely crystalloids and/or colloids, and if crystalloids, Ringer's lactate or normal saline, as well as in terms of rate of administration. While crystalloids appear to be the ideal choice based on expert opinion and the guidelines/ recommendations from America, Italy and Japan, these recommendations are not based on high-level evidence in patients with acute pancreatitis (18, 19, 21-25, 28, 29). In patients with severe acute pancreatitis, the two randomized trials available used a combination of crystalloids and colloids, and favoured controlled resuscitation over rapid infusion within the first 72 hours (26, 27). Considering that both of these trials were performed by the same group, these results need to be validated by other groups. There has been no further impetus even in animal studies since the last major review by Gardner et al. (32).

Conclusion

Fluid therapy remains the mainstay of early management of patients with acute pancreatitis and severe acute pancreatitis. High-level evidence is lacking to guide protocols for fluid resuscitation in patients presenting with acute pancreatitis. In those patients with severe acute pancreatitis, the available evidence indicates that controlled fluid resuscitation with crystalloids and colloids offers the best outcome. Hematocrit remains a useful marker to guide fluid resuscitation in acute pancreatitis. However, the timing and ideal "cut-off" level need to be determined.

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TERAPIJA TEČNOSTIMA KOD AKUTNOG PANKREATITISA

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Neposredno nakon postavljanja dijagnoze akutnog pankreatitisa, neophodan je suštinski terapijski tretman, što uključuje monitoring stanja svesti, respiratornog i kardiovaskularnog sistema, diureze, adekvatnu nadoknadu volumena tečnostima, kontrolu bola, purifikacionu terapiju krvi i nutricionu potporu. Adekvatna količina nadoknade fluida je esencijalna za stabilizaciju kardiovaskularne dinamike, a količina se prilagođava dok se ne postigne stabilnost i konstantnost cirkulatorne dinamike. Dosadašnji vodiči kliničke prakse preporučivali su agresivnu nadoknadu fluida, uprkos limitiranim prospektivnim podacima koji bi te preporuke potvrdili. Terapija fluidima ostaje kamen temeljac ranog tretmana bolesnika sa akutnim pankreatitisom i teškim akutnim pankreatitisom. Ne postoje precizni protokoli i klinički vodiči visokog nivoa tečnosti za rasuscitaciju bolesnika sa akutnim pankreatitisom. Kod bolesnika sa teškim akutnim pankreatitisom, dostupni podaci preporučuju kontrolisanu nadoknadu fluida, što omogućava najbolji oporavak bolesnika. Hematokrit ostaje koristan pokazatelj pri nadoknadi fluida u akutnom pankreatitisu. Međutim, vreme i idealna referentna vrednost tek treba da budu determinisani. *Acta Medica Medianae 2013;52(3):55-60.*

Ključne reči: *akutni pankreatitis, vodiči, reanimacija*

