

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2023 May 5; 14(3): 22-32





MINIREVIEWS

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World Journal of Gastrointestinal Pharmacology and Therapeutics

Bimonthly Volume 14 Number 3 May 5, 2023

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INDEXING/ABSTRACTING

The WJGPT is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yu; **Production Department Director:** Xiang Li; **Editorial Office Director:** Jin-Li Wang.

NAME OF JOURNAL

World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN

ISSN 2150-5349 (online)

LAUNCH DATE

May 6, 2010

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Emanuele Sinagra

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2150-5349/editorialboard.htm>

PUBLICATION DATE

May 5, 2023

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ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

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Update on the strategy for intravenous fluid treatment in acute pancreatitis

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Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): D, D

Grade E (Poor): E

P-Reviewer: Gong F, China; Kitamura K, Japan; Liu C, China

Received: February 12, 2023

Peer-review started: February 12, 2023

First decision: March 7, 2023

Revised: March 21, 2023

Accepted: April 18, 2023

Article in press: April 18, 2023

Published online: May 5, 2023



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Abstract

Fluid therapy/resuscitation is mandatory in acute pancreatitis due to the pathophysiology of fluid loss as a consequence of the inflammatory process. For many years, without clear evidence, early and aggressive fluid resuscitation with crystalloid solutions (normal saline solution or Ringer lactate solution) was recommended. Recently, many randomized control trials and meta-analyses on fluid therapy have revealed that high fluid rate infusion is associated with increased mortality and severe adverse events compared to those resulting from moderate fluid rates, and this has triggered a paradigm shift in fluid management strategies. Meanwhile, there is evidence to show that Ringer lactate solution is superior to normal saline solutions in this context. The purpose of this review is to provide an update on the strategies for intravenous fluid treatment in acute pancreatitis, including the type, optimal amount, rate of infusion, and monitoring guides. Recommendations from recent guidelines are critically evaluated for this review in order to reach the authors' recommendations based on the available evidence.

Key Words: Acute pancreatitis; Fluid resuscitation; Aggressive fluid resuscitation; Moderate fluid resuscitation; Crystalloids; Colloids

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Core Tip: The standard care for patients with acute pancreatitis is fluid therapy. According to many randomized control trials, early and non-aggressive/moderate fluid resuscitation is preferable to aggressive fluid resuscitation. An excessive amount of fluid resuscitation has been found to cause more vascular leakage, which worsens pancreatic local complications and increases infection and pulmonary complications. Ringer lactate solutions are administered as the fluid of choice in this setting to maintain adequate hemodynamic status, with a mean arterial pressure of ≥ 65 mmHg and urine output of ≥ 0.5 mL/kg/h used as the initial fluid resuscitation goal.

Citation: Yaowmaneerat T, Sirinawasatien A. Update on the strategy for intravenous fluid treatment in acute pancreatitis. *World J Gastrointest Pharmacol Ther* 2023; 14(3): 22-32

URL: <https://www.wjgnet.com/2150-5349/full/v14/i3/22.htm>

DOI: <https://dx.doi.org/10.4292/wjgpt.v14.i3.22>

INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas with a variable disease course, ranging from mild self-limiting to progressive severe disease resulting in multiple organ failure with high rates of morbidity and mortality. Among patients admitted with acute pancreatitis, around 80% have a mild clinical course; however, the others develop serious illness, with a mortality rate of approximately 20% [1]. No proven pharmacological therapy currently exists to treat acute pancreatitis; however, intravenous (IV) fluid resuscitation is recommended as a fundamental component of initial supportive treatment in order to reduce morbidity and mortality for patients with this condition [2]. Several studies published in the last decade have raised concerns about the efficacy and safety of early aggressive fluid resuscitation in the treatment of acute pancreatitis. Many clinical guidelines for acute pancreatitis recommend vigorous early fluid resuscitation, but over-aggressive fluid therapy can result in poor clinical outcomes, in particular respiratory complications [3] and abdominal compartment syndrome [4]. The objective of this narrative review is to update the most recent evidence on intravenous fluid treatment strategies, as well as to propose the goals of resuscitation and monitoring in patients with acute pancreatitis.

PATHOPHYSIOLOGICAL BASIS

Mortality in severe acute pancreatitis is largely caused by remote organ failure due to activation of excessive pro- and anti-inflammatory mediators and systemic inflammatory response syndrome (SIRS) [5]. Overexpressed inflammatory mediators, such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-8, will injure the microcirculation endothelium and then increase the permeability of vasculature, resulting in the transudation of fluid from the intravascular to the third space, leading to capillary leakage syndrome and multiple organ dysfunction syndrome [6]. Other consequences of acute pancreatitis are nausea and vomiting with poor intake of adequate amounts of fluids, leading to the intensification of intravascular volume depletion.

In addition, levels of vasoactive mediators and procoagulant factors are increased in acute pancreatitis, probably triggered by inflammatory mediators, promoting capillary vasoconstriction and microthrombi formation [2]. Impaired pancreatic microcirculation *via* increasing capillary permeability, vasospasm, and the formation of microthrombi, have a significant impact on the early stages of the disease and have been implicated as a major contributor to the pathogenesis of pancreatic necrosis [2,6]. Therefore, the goal of effective fluid resuscitation is to restore blood volume deficiency and block the microcirculatory disorder in the early stages of the disease in order to prevent local and systemic complications [6].

Severity grading of acute pancreatitis and risk stratification

The revised Atlanta classification for acute pancreatitis categorizes the disease into two types (interstitial edematous and necrotizing pancreatitis), while the severity is measured on a three-grade scale: Mild (having no local or systemic complications and no organ failure); moderately severe (the presence of local or systemic complications and/or organ failure that resolves within 48 h); and severe (having organ failure that persists for over 48 h) [7]. Interstitial edematous subtypes are usually associated with mild severity, whereas necrotizing pancreatitis is commonly seen in patients with moderately severe or severe acute disease. Three organ systems, the respiratory, kidney, and cardiovascular systems, should be assessed for organ failure based on the modified Marshall scoring system (Table 1) [8]. Mortality in acute pancreatitis occurs early in the course of the disease, and the presence of persistent multi-organ

Table 1 Modified Marshall scoring system for organ dysfunction

Organ system	Score ^a				
	0	1	2	3	4
Respiration (PaO ₂ /FiO ₂) ^b	> 400	301-400	201-300	101-200	< 101
Kidney (serum creatinine), μmol/L	< 134	134-169	170-310	311-439	> 439
Kidney (serum creatinine), mg/dL	< 1.4	1.4-1.8	1.9-3.6	3.7-4.9	> 4.9
Cardiovascular (systolic blood pressure), mmHg	> 90	< 90, fluid responsive	< 90, not fluid responsive	< 90, pH < 7.3	< 90, pH < 7.2

^aScore ≥ 2 for any system defines the presence of organ failure.

^bFor nonventilated patients, FiO₂ can be estimated by the rate of supplemental oxygen (Room air, 21%; 2 L/min, 25%; 4 L/min, 30%; 6-8 L/min, 40%; 9-10 L/min, 50%).

FiO₂: Fraction of inspired oxygen; PaO₂: Partial pressure of arterial oxygen.

failure is the key determining factor[9].

Multiple scoring systems have been developed to predict severity and guide management according to the anticipated severity of the disease[10]. Earlier scoring systems, such as the Ranson or Imrie-Glasgow, need to be completed 48 h after admission, which is outside the critical period of the first 12-24 h of hospitalization, where the highest incidence of organ failure occurs[11]. The Acute Physiology and Chronic Health Examination (APACHE) II score, which includes initial values of 12 routine physiologic measurements, including age and chronic health status, was originally developed to predict disease severity and mortality for critically ill patients in intensive care units[12]. It is extensively used in acute pancreatitis to forecast severe disease, with good negative predictive and modest positive predictive values. However, its limitations are that it is complex and cumbersome to use, along with the fact that these variables are not obtained on a regular basis from patients who are not critically ill[13].

The Bedside Index for Severity in Acute Pancreatitis (BISAP) score has been developed to predict in-hospital mortality. The presence of each of the following parameters during the first 24 h is assigned 1 point: Blood urea nitrogen (BUN) > 25 mg/dL; impaired mental status; SIRS; age > 60 years; and the presence of pleural effusion. Patients with a score of 0 have been found to have a mortality rate of < 1%, compared with 22% in those with a score of 5[14]. A cohort of 397 patients found that a BISAP score ≥ 3 was associated with an increased risk of developing organ failure [odds ratio (OR) 7.4, (95%CI: 2.8-19.5)], persistent organ failure (OR 12.7, 95%CI: 4.7-33.9), and pancreatic necrosis (OR 3.8, 95%CI: 1.8-8.5)[15]. In addition, a validation study of the BISAP score which included 185 patients demonstrated that its performance was similar to those of Ranson's, APACHE II, and CT severity index scores in predicting organ failure, complications, and mortality[16]. It is thus widely used because its components are clinically relevant and easily calculated at the bedside.

STRATEGY FOR INTRAVENOUS FLUID TREATMENT

Intravenous hydration or resuscitation is the standard treatment for patients with acute pancreatitis of any severity, to correct hypovolemia and maintain intravascular volume for better tissue perfusion in order to prevent pancreatic microcirculation ischemia and reduce local complications. Fluid hydration needs to be maintained in the early phase to prevent the cascade of events resulting in pancreatic necrosis[2]. A retrospective study found that early fluid resuscitation was associated with a decreased incidence of SIRS and organ failure at 72 h[17]. Hemoconcentration, a marker of hypovolemia, on admission together with persistent 24-hour hemoconcentration, have been found to be associated with the development of necrotizing pancreatitis and organ failure[18]. Many recommendations for fluid replacement are based on observational and retrospective studies conducted since the 1990s which found that it was associated with a reduction in morbidity and mortality[19,20]. At present, there are no clearly defined details of the type, fluid flow rate, total volumes, or goal of resuscitation[21].

Which patient

Fluid replacement is the mainstay treatment recommended for every patient with acute pancreatitis of any severity. It shows benefits in both mild and severe forms of the disease, as confirmed by a single-center randomized controlled trial (RCT) from Buxbaum *et al*[22] of patients with the mild acute pancreatitis, and a study of patients with the severe form by Yamashita *et al*[23]. The latter, which was a multicenter retrospective study of 1097 severe acute pancreatitis patients, revealed that fluid replacement volume > 6 L within the first 24 h was significantly associated with decreased mortality (OR 0.58; *P* < 0.05). However, this treatment may have limitations in patients with underlying disease not included in clinical trials due to the risk of fluid overload. The majority of studies have excluded

patients who had the following: Known history of renal disease (such as those with basal creatinine > 2 mg/dL or who had undergone chronic hemodialysis); greater than the New York Heart Association class II heart failure; chronic lung disease requiring supplemental home oxygen; active acute infection (including acute cholecystitis and acute cholangitis); hypernatremia (serum sodium > 145 mEq/L); hyponatremia (serum sodium < 135 mEq/L); or hyperkalemia (serum potassium > 5 mEq/L)[24]. The patients in this group require individualized assessment and need to be closely monitored[25].

Which fluid

The fluid of choice for rehydration is the isotonic crystalloid solution, which contains normal saline (NS) and balanced/buffered crystalloid [such as lactated Ringer's (LR), Plasma-Lyte, or Hartmann's solution]. NS and LR are most widely used as a first-line solution in acute pancreatitis. The chloride concentration of NS (154 mEq/L) is higher than those of LR (109 mEq/L) and human plasma (94-111 mEq/L)[26]. Infusion of NS generally causes hyperchloremic metabolic acidosis which is dose-dependent[27]. The effect of hyperchloremia on renal function was examined by Chowdhury *et al*[28] who revealed a significant reduction from baseline in mean renal blood flow velocity ($P = 0.045$) and renal cortical tissue perfusion ($P = 0.008$) after NS intravenous infusion but not with Plasma-Lyte. Furthermore, chloride load may increase renal inflammation and impair renal perfusion, leading to acute kidney injury and increased risk of renal replacement therapy[28,29].

Regarding clinical evidence of fluid resuscitation using LR and NS, Zhou *et al*[30] performed a meta-analysis of 4 RCTs which made direct comparisons between LR and NS resuscitation in 248 patients, and they found that the LR group was at lower risk of developing moderately severe/severe pancreatitis [OR 0.49, (95%CI: 0.25-0.97)]. In addition, the LR group was less likely than the NS group to require intensive care unit (ICU) admission [OR 0.33, (95%CI: 0.13-0.81)] or develop local complications, defined as a composite of acute peripancreatic fluid collection, pancreatic necrosis, peri-pancreatic necrosis, pancreatic pseudocyst, and walled-off necrosis [OR 0.42, (95%CI: 0.2-0.88)]. Meanwhile, there is conflicting evidence regarding whether the use of LR is associated with an anti-inflammatory effect, as shown by the reduction of C-reactive protein levels and incidence of SIRS, as compared with NS[24,31-33].

The recent evidence favoring balanced crystalloids (LR or Plasma-Lyte) over NS is based on two large RCTs that were conducted in 2018. The first by Semler *et al*[29], the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) study of critically ill adults, found that the use of balanced crystalloids for intravenous fluid administration can reduce the composite outcome of in-hospital mortality, new renal replacement therapy, and persistent renal dysfunction compared with the use of NS [(OR 0.90, (95%CI: 0.82-0.99); $P = 0.04$]. Another study by Self *et al*[26], the Saline Against Lactated Ringer's or plasma-lyTe in the Emergency Department trial, investigated the effect of intravenous crystalloids replacement among noncritically ill patients in the emergency department who were subsequently hospitalized outside an ICU. This study revealed that, compared with NS, the balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days [4.7% *vs* 5.6%; adjusted OR 0.82, (95%CI: 0.70-0.95); $P = 0.01$].

The use of colloids should be avoided given the absence of demonstrable benefits in terms of decreased mortality and possible increased risk of organ failure[6,34]. The colloid solutions can be divided into two groups: 'semi-synthetic' [hydroxyethyl starch (HES), gelatin, and dextran solutions]; and 'natural' (human albumin solution). Colloids are IV fluids that contain high molecular weight, microscopic substances suspended in crystalloid solutions which have the theoretical ability to stay in the intravascular space longer than crystalloids due to oncotic pressure from macromolecules in solution. HES is the most frequently used colloid, and a small RCT by Xiao *et al*[35] showed that resuscitation with HES compared to LR can decrease the risk of intra-abdominal hypertension and reduce the need for mechanical ventilation in severe acute pancreatitis patients. The data from a large RCT comparing HES with NS resuscitation in 7000 patients in the ICU, revealed no survival benefit of HES and found that it actually resulted in increased use of renal replacement therapy [RR 1.21, (95%CI: 1.00-1.45); $P = 0.04$][36]. A recent meta-analysis by Di Martino *et al*[37] found that in comparison with the use of HES, NS reduced the number of severe adverse events [RR 0.38, (95%CI: 0.27-0.54); $P < 0.001$] and organ failure [RR 0.30, (95%CI: 0.21-0.44); $P < 0.001$][37]. Human serum albumin infusion, a common fluid given to acute pancreatitis patients admitted to the ICU, has no proven benefits. A recent large retrospective cohort study comparing patients who received human serum albumin infusion ($n = 228$) to those who did not ($n = 772$) found that it did not reduce in-hospital mortality and was, in fact, associated with longer hospital and ICU stays. The study also revealed that the outcome was unaffected by initial serum albumin levels, infections, or total amount or initial timing of infusion[38].

As a result, we opted for LR as the first choice for fluid therapy over NS, agreeing with many other guidelines in recommending against the use of HES for IV resuscitation in patients with acute pancreatitis[34,39].

Rate and volume

While early and aggressive fluid resuscitation has been discussed in many studies in the literature and is recommended by many guidelines[19,40], the optimal volumes and rates of fluid replacement are still unknown. To date, the early resuscitation period has been reduced to a 4-6 h therapeutic window from

the initial hospital presentation. Evidence from a large multicenter retrospective study by Singh *et al*[41] demonstrated that early fluid resuscitation > 1 L in the first 4 h compared with < 0.5 Liter in the first 4 h was associated with a significantly lower need for interventions. It has been estimated that fluid sequestration in the first 48 h is 3.7 L in mild pancreatitis and 5.6 L in severe pancreatitis[42]. In addition, baseline predictors for a higher volume of fluid sequestration have been found to be younger age, high hematocrit, high blood glucose, SIRS ≥ 2 , and history of excessive alcohol consumption, and it has been suggested that these factors can help to identify patients who need more aggressive fluid resuscitation[43].

The first RCT to analyze the optimal fluid therapy issue was conducted by Mao *et al*[44] in 2009, and they found that aggressive fluid resuscitation (rate 10-15 mL/kg/h *vs* 5-10 mL/kg/h) increased mortality and complications, including respiratory failure, abdominal compartment syndrome, and sepsis. Subsequently, many RCTs have been conducted with reduced rates of IV fluid, but these studies revealed no benefit of aggressive IV hydration and have instead identified its harmful effects, as shown in Table 2. A recent meta-analysis by Di Martino *et al*[37] included 4 RCTs that compared aggressive rate *vs* moderate rate of resuscitation and found that, compared with moderate fluid rate infusion, high fluid rate infusion was associated with increased mortality [OR 2.88, (95%CI: 1.41-5.88); $P = 0.004$], higher numbers of severe adverse events [RR 1.42, (95%CI: 1.04-1.93); $P = 0.030$], and increased incidence of sepsis [RR 2.80, (95%CI: 1.51-5.19); $P = 0.001$].

Specifically investigating patients with mild pancreatitis, a previous RCT conducted by Buxbaum *et al* [22] showed that aggressive fluid hydration appeared to be effective. However, a recent large RCT, the WATERFALL study, in which 249 patients with mild pancreatitis were included in the interim analysis, was conducted to compare aggressive (bolus 20 mL/kg, then infusion 3 mL/kg/h) and moderate (preceded by bolus 10 mL/kg only if the patient had hypovolemia, then infusion 1.5 mL/kg/h) fluid resuscitation. The median volume of fluid given during the first 48-h period was higher in the aggressive-resuscitation group than in the moderate-resuscitation group (7.8 *vs* 5.5 L). The study terminated early owing to safety issues regarding whether aggressive fluid resuscitation was harmful, as it resulted in a higher incidence of fluid overload (20.5%) in the aggressive-resuscitation group compared with 6.3% in the moderate-resuscitation group, adjusted [RR 2.85; (95%CI: 1.36-5.94), $P = 0.004$], while no statistical significance was observed in the development of moderately severe or severe pancreatitis during hospitalization[47].

In the absence of conclusive high-quality evidence, society guidelines have recommended various fluid resuscitation approaches for acute pancreatitis. Many guidelines recommend early aggressive fluid therapy without providing full details[19,40]. The American College of Gastroenterology (ACG) recommended the use of an aggressive hydration rate of 250-500 mL/h in the first 12-24 h[48]. Japanese guidelines issued in 2015 recommended short-term rapid fluid resuscitation for patients in shock or with dehydration (150-600 mL/h depending on the hemodynamics status) during the early stages of acute pancreatitis, while 130-150 mL/h of optimal fluid infusion rate was advised for those without dehydration[25]. Although the revised Japanese guidelines of 2021 recommended aggressive fluid resuscitation as initial therapy, they omitted information on the rate at which the fluids should be administered[40]. On the other hand, utilizing "goal-directed" fluid resuscitation has been advised by both the American Gastroenterological Association[34] and the International Association of Pancreatology/American Pancreatic Association (IAP/APA)[39]. Additionally, a starting IV rate of 5-10 mL/kg/h has been suggested until resuscitation goals have been met[39].

Based on the available evidence, we recommend a moderate fluid resuscitation strategy, beginning with LR IV rate of 1.5 mL/kg/h in the first 24-48 h, preceded by a bolus of 10-20 mL/kg in 1-2 h if patients have moderately severe to severe pancreatitis, hypovolemia, signs of dehydration, acute kidney injury, or poor predictive indicators, such as BUN > 25 mg/dL or hematocrit $\geq 44\%$ (Table 3).

Goal and monitoring

The goal of fluid resuscitation is to correct hypovolemia and improve organ and tissue perfusion by increasing intravascular volume in order to increase cardiac output and reduce complications[27,49]. Response to fluid resuscitation depends on cardiac function, baseline preload, and duration of intravascular volume expansion. In critically ill patients, especially those with sepsis, severe trauma, or acute pancreatitis, the inflammatory process and cytokines damage the endothelial glycocalyx leading to alterations in vascular permeability resulting in increased capillary leakage and loss of albumin. It triggers increased rates of fluid loss from the intravascular to the extravascular space, which causes depletion in intravascular volume, so that a bolus dose or maintenance of fluid hydration is needed[27]. Accordingly, volume status requires interval assessment to balance the risk of volume overload against the risk of hypovolemia from fluid leakage, insensible loss, poor intake, and vomiting, particularly in severe pancreatitis[50,51].

Goal-directed fluid treatment, which is defined as the use of several parameters and perfusion targets to guide the titration of fluid administration, has been used in multiple studies and guidelines as a key concept[34,39], and it has been shown to improve survival rates in patients with sepsis and septic shock [52]. Four RCTs with various fluid administration methods used goal-directed therapy for acute pancreatitis, but no obvious benefit was revealed[34]. Another study, however, suggested that goal-directed fluid treatment may be associated with increased survival. Wang *et al*[53] conducted a prospective study

Table 2 Summary of randomized controlled trials comparing different intravenous fluid resuscitation strategies in acute pancreatitis

Ref.	Design	N	Participants	Randomization	Aggressive resuscitation	Volume	Nonaggressive resuscitation	Volume	Effect of early aggressive resuscitation
Mao <i>et al</i> [44], 2009	Superiority	76	Severe AP	72 h	Rapid volume expansion (10-15 ml/kg/h)	4 ± 2 L Crystalloid; 1.3 ± 0.8 L; Colloid in 24 h	Controlled volume expansion (5-10 ml/kg/h)	2.4 ± 1.9 L Crystalloid; 0.9 ± 0.6 L; Colloid in 24 h	Harmful, more sepsis, mortality, mechanical ventilation, and ACS
Mao <i>et al</i> [46], 2010	Superiority	115	Severe AP	24 h	Rapid hemodilution with goal Hct < 35% at 48 h	-	Slow hemodilution with goal Hct > 35% at 48 h	-	Harmful, more sepsis, and mortality
Wu <i>et al</i> [31], 2011	Factorial	40	Any severity	6 h	Goal-directed with 20 ml/kg bolus + 3 or 1.5 ml/kg/h of LR or NS	4.3 L in 24h	LR or NS fluid therapy adjusted by treating physician	4.6 L in 24h	Similar, SIRS, and CRP at 24 h
Buxbaum <i>et al</i> [22], 2017	Superiority	60	Predicted mild AP	4 h	20 ml/kg bolus + 3 ml/kg/h of LR	5.6 L in 24 h; 7.6 L in 36 h	10 ml/kg bolus then 1.5 ml/kg/h of LR	3.9 L in 24 h; 5.6 L in 36 h	Beneficial, less composite outcome, SIRS, and hemoconcentration
Cuéllar-Monterrubio JE <i>et al</i> [45], 2020	Two-tailed	88	Any severity AP, more than 24 hr disease onset	4 h	20 mL/kg bolus + 3 mL/kg/hr first 24 hours and then 30 mL/kg for the next 24 hours	8.54 ± 1.83 L in 48 h	20 ml/kg bolus (if hypovolemia, 3/45) - 1.5 ml/kg/h of HS first 24 hours and then 30 mL/kg for the next 24 hours	5.13 ± 1.28 L in 48 h	No benefit, no differences found in SIRS, pancreatic necrosis, Respiratory complication, AKI, and LOS
De-Madaria E <i>et al</i> [47], 2022	Two-tailed	249	Mild AP, less than 24 h disease onset	8 h	20 ml/kg bolus + 3 ml/kg/h of LR	7.8 (6.5-9.8) L in 48h	10 mL/kg bolus (if hypovolemia) - 1.5 ml/kg/h of LR	5.5 (4.0-6.8) L in 48 h	Harmful, more fluid overload

AP: Acute pancreatitis; ACS: Abdominal compartment syndrome; LR: Lactated Ringer's; NS: Normal saline; SIRS: Systemic inflammatory response syndrome; CRP: C-reactive protein; HS: Hartmann's solution; AKI: Acute kidney injury; LOS: Length of stay.

using the goal-directed objectives of fluid resuscitation during the first 6 h of severe acute pancreatitis individuals who were admitted to the ICU within 24 h of the onset of the disease. Objectives should include all of the following: central venous pressure (CVP) 8-12 mmHg; mean arterial pressure (MAP) ≥ 65 mmHg; urine output ≥ 0.5 mL/kg/h; and central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70%. The study showed that goal-directed therapy reduced mortality in patients with severe acute pancreatitis[53].

Laboratory tests for determining volume status and sufficient tissue perfusion include measuring hematocrit, BUN, creatinine (Cr), and lactate[19]. Acute renal injury is caused by reduction of intravascular volume together with a direct renal injury mechanism occurring in acute pancreatitis, which is facilitated by the leak of activated enzymes such as trypsin and chymotrypsin, inflammatory mediators, and cytokines; these are the reasons for increased BUN in acute pancreatitis patients[54]. An elevated BUN has been used as a marker of severe disease, whereas a declining BUN indicates improving renal perfusion and adequate resuscitation; therefore, the point at which the BUN level decreases or is normalized is used as the endpoint of a goal-directed fluid resuscitation protocol[31].

Hematocrit has long been used to guide fluid replacement in critically ill patients, and it has also been identified as a marker that correlates with the development of pancreatic necrosis in acute pancreatitis [18,55]. Brown *et al* [56] previously demonstrated that hemoconcentration, with a hematocrit of ≥ 44% on admission or failure of hematocrit to decrease at 24 h, was associated with the development of necrotizing pancreatitis[56]. A recent retrospective study from a prospective database of 628 patients also found that hemoconcentration at baseline or an increase in hematocrit at 24 h was associated with persistent organ failure (OR = 2, *P* = 0.03)[57].

Elevated serum lactate should be considered as a factor for guidance in the treatment of critically ill patients, since it is well-recognized as a marker of tissue hypoxia/hypoperfusion, as well as a marker of resuscitation in the setting of unstable hemodynamics, and it should be monitored[19], although there is no evidence to support its relevance in patients with acute pancreatitis. Unfortunately, other serum biomarkers, such as brain natriuretic peptide, neutrophil gelatinase-associated lipocalin (NGAL), and intestinal fatty acid-binding protein (I-FABP), fail to differentiate between fluid responsive and

Table 3 Authors' recommendations for fluid resuscitation strategy in acute pancreatitis

Parameter	Recommendation
Who	All patients with any severity
Timing	Early fluid resuscitation is better
Type of fluid	Ringer lactate solutions better than normal saline solutions Avoid synthetic colloids (HES or Dextran), Limited data in human albumin
Amount of fluid	
Mild pancreatitis	3 L in 24 h and 4-6 L in 48 h
Moderate or severe pancreatitis	3-4 L in 24 h and 6-8 L in 48 h based on clinical/lab parameters
Rate of infusion	
Mild pancreatitis	1.5 mL/kg/h with bolus dose 10 mL/kg/h in 1-2 h in patients with hypovolemia, BUN > 25, Hematocrit \geq 44%, AKI, Age < 40 yr, and Alcoholic etiology
Moderate or severe pancreatitis	1.5-3 mL/kg/h with bolus dose 10-20 mL/kg/h in 1-2 hours or higher in hypotension
Monitoring goals	MAP \geq 65 mmHg, Urine output \geq 0.5 mL/kg/h Hematocrit < 44% and/or BUN < 25 mg/dL at 12 and 24 h (for guided fluid rate adjustment) Invasive monitoring and dynamic parameters needed in ICU patients or cardio/renal dysfunction patients
Duration	24-48 h, Infusion can stop after 24 h if oral feeding can be tolerated in mild pancreatitis

HES: Hydroxyethyl starch; BUN: Blood urea nitrogen; AKI: Acute kidney injury; MAP: Mean arterial pressure.

refractory patients[49].

In cases of severe pancreatitis with organ failure in the ICU, when fluid restriction is warranted due to renal or cardiac dysfunction, an invasive clinical assessment is required. A single clinical sign or non-invasive clinical assessment cannot accurately reflect volume status, and the use of multiple parameters measured by an invasive technique is more reliable[58]. CVP is a traditional static parameter that is often used in general practice in order to indicate volume status and preload responsiveness[59]. However, in severe pancreatitis, it may not be as good a parameter as septic shock, since massive fluid extravasation (pleural effusion, ascites), frequently leads to falsely high CVP values from increased intrathoracic and intraabdominal pressure, resulting in under-resuscitation when employing CVP-based algorithms[60].

Dynamic parameters and tests (*e.g.*, passive leg raising test) that measure cardiac response with changes in preload, such as stroke volume variation and pulse pressure variation, are better predictors of volume status and fluid responsiveness. A pilot study was recently conducted by Jin *et al*[61] to evaluate a strategy for optimizing fluid requirements following initial resuscitation in individuals with predicted severe acute pancreatitis. It was designed for serial monitoring of an objective clinical assessment of volume status (heart rate, mean arterial pressure, urine output, and hematocrit), and to measure the changes in stroke volume in response to a mini-fluid challenge (250 mL over 10 min) and the passive leg-raising test. They found that a mini-fluid challenge and the resulting change in stroke volume can be used as the goal to determine the rate of IV fluid therapy (5-10 *vs* 1-3 mL/kg/h). Additionally, the passive leg-raising test was superior to an objective clinical assessment of volume status for predicting fluid responsiveness and guiding fluid therapy, and it is therefore noteworthy of further study in this regard[61].

According to the IAP/APA 2013 guidelines for the management of acute pancreatitis, the aim of fluid resuscitation should be based on one or more of the following: (1) Non-invasive clinical targets (heart rate < 120/min, mean arterial pressure 65-85 mmHg, and urinary output > 0.5-1 mL/kg/h; (2) Invasive clinical targets of stroke volume variation, and intrathoracic blood volume determination; and (3) Biochemical targets of hematocrit 35%-44%[39]. Meanwhile, Japanese guidelines of 2015 recommended that after rapid fluid resuscitation, until MAP \geq 65 mmHg and urine output \geq 0.5 mL/kg/h are reached, IV fluid should be given at a slower rate and adjusted to maintain these targets. These guidelines also stated that decreases in BUN, hematocrit, and CVP did not serve as useful indicators for discontinuation of fluid resuscitation[25]. Evidence from nationwide surveys in Japan in 2011 and 2016, showed that compliance with acute pancreatitis bundles for the early management (within the first 48 h) of patients with severe acute pancreatitis, using a MAP \geq 65 mmHg and a urine output \geq 0.5 mL/kg/h as adequate resuscitation targets, can improve patient survival rates[62-64].

We recommend using a MAP ≥ 65 mmHg and a urine output ≥ 0.5 mL/kg/h as a goal for the initial phase of fluid resuscitation based on the available data. An interval clinical assessment to check for signs of dehydration/volume overload and to maintain MAP ≥ 65 mmHg and urinary output ≥ 0.5 mL/kg/h is essential. Fluid rate adjustments during the maintenance phase should be guided by the biochemical targets of hematocrit of 35%-44% at 12 and 24 h after disease onset (Table 3).

CONCLUSION

Fluid therapy/resuscitation is currently the mainstay treatment for acute pancreatitis. Non-aggressive fluid resuscitation is a new paradigm shift in fluid management that is recommended and should be considered. The preferred fluid is the Ringer lactate solution, with MAP ≥ 65 mmHg and urine output ≥ 0.5 mL/kg/h as the initial fluid resuscitation goal. There is still insufficient evidence to establish the best strategy for fluid optimization after initial resuscitation in patients who have severe pancreatitis or who require fluid restriction due to cardio or renal dysfunction. While hemoconcentration is a poor predictor, serial hematocrit can guide fluid adjustment by maintaining a target hematocrit of $< 44\%$.

FOOTNOTES

Author contributions: Yaowmaneerat T searched the literature and drafted the manuscript; Sirinawasatien A devised the project with the main conceptual ideas and performed manuscript revisions; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have declared that no competing interests exist.

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S-Editor: Ma YJ

L-Editor: A

P-Editor: Yu HG

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