Fluid Therapy in Acute Pancreatitis

Anybody's Guess

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Objective: The aim of this study was to systematically review and evaluate the quality of current evidence about fluid therapy (FT) in acute pancreatitis (AP).

Background: Intravenous FT is thought to be important in the early management of patients with AP. Clinically relevant questions remain regarding the type of fluid, the rate of administration, and the goal of FT.

Methods: A comprehensive literature search for human studies was performed using online databases (MEDLINE, EMBASE, PubMed, and the Cochrane Library). The quality of the entire body of evidence was then graded according to the Grading of Recommendations Assessment, Development and Evaluation Working Group guidelines in relation to 3 key areas: type of fluid, rate of fluid administration, and goal-directed FT.

Results: The initial search yielded 410 studies, of which 15 met the inclusion criteria. Only 2 randomized studies compared types of fluids. Nine studies looked at aggressive versus nonaggressive resuscitation protocols, of which 4 concluded that an aggressive approach yielded better outcomes and 5 concluded that a nonaggressive approach was better. Two studies investigated goal-directed FT, using different goals; one demonstrating benefit and the other none. Analysis of the body of evidence as per the Grading of Recommendations Assessment, Development and Evaluation Working Group revealed that the majority of evidence was of low or very low quality.

Conclusions: FT is considered a cornerstone of the early management of patients with AP and yet the evidence on which it is based remains paltry and of poor quality. This systematic review has demonstrated the equipoise necessary for the design of randomized controlled trials to answer pressing questions relating to the type of fluid, the rate of administration, and how FT should be guided.

Keywords: acute pancreatitis, fluid therapy, goal-directed, GRADE, resuscitation, review

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Acute pancreatitis (AP) remains a substantial clinical challenge, with a wide range of causes, severity, protean local and systemic complications, and the absence of specific therapy targeting the underlying pathophysiology.[1–3] As a result, the management of AP remains largely supportive, and during the early phase, the cornerstone of this is believed by many to be fluid therapy (FT). The risk of hypovolemia secondary to third-space fluid loss has long been recognized, and the prevention or early correction of it by intravenous fluid resuscitation is universally recommended.[4]

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The risk of hypovolemia and associated complications provides the rational behind the fact that the majority of clinical practice guidelines advocate aggressive approaches to fluid resuscitation, but there is a lack of consensus on specific recommendations regarding the type of fluid to use, the optimal rate of fluid administration, and what goals to use for indicating adequate resuscitation.[5,6] Adding further to the confusion surrounding FT in AP is recent evidence suggesting that a nonaggressive approach to resuscitation may reduce mortality and improve outcomes.[7–11] In light of this dissonance, the evidence base for FT in AP has been systematically reviewed here to help determine the way forward. The aim of this review was therefore to critically evaluate current evidence with regard to FT in AP, including a formal appraisal of evidence quality.

METHODS

Literature Search

A systematic and comprehensive search of major reference databases (MEDLINE, EMBASE, PubMed, and the Cochrane Library) was undertaken using the search string "exp Pancreatitis/AND exp Fluid Therapy/." This search string explodes the subject headings of pancreatitis and FT incorporating all subheadings, thereby providing a comprehensive search strategy. The search was restricted to human evidence published since 1990 but was not language restricted. Articles were compiled into a database and duplicates were removed. The abstracts were then screened for relevance. Subsequently, the reference lists of relevant trials, reviews, and international guidelines were hand-searched.

Inclusion and Exclusion Criteria

Inclusion criteria were all human studies (randomized, prospective observational, and retrospective observational) investigating FT when all participants were patients with AP. The articles that did not report on the role and use of FT in AP were excluded. The search and the decision to include or exclude articles were done by 2 authors (M.D.H., H.W.), with uncertainties referred to a third author (A.M.).

Data Abstraction and Analysis

The data were abstracted onto a pro forma that included the study setting, study design, Oxford centre for evidence based medicine level of evidence,[12] number of participants, type of fluid used, rate of administration, primary endpoint, secondary endpoints, and resuscitation goals. For the purposes of this review, any study that specified rapid resuscitation was classified as aggressive FT whereas any study that specified controlled resuscitation was classified as nonaggressive FT.

Grading of Evidence

The entire body of evidence was critically evaluated by 2 authors (M.D.H., H.W.), with disagreements referred to a third author (A.M.) as per the Grading of Recommendations Assessment, Development and Evaluation guideline for quality using the GRADEpro

software.[13] The process established by the Grading of Recommendations Assessment, Development and Evaluation Working Group[14–19] to evaluate bodies of evidence requires comparisons to be decided upon; in this study the 3 comparisons used were type of fluid, nonaggressive versus aggressive fluid resuscitation, and goal-directed versus non–goal-directed FT. For each comparison, outcomes were then decided upon and the evidence for each outcome was graded. The following outcomes were investigated for each of the 3 comparisons: systemic inflammatory response syndrome, organ dysfunction (emerging and/or persistent), development of pancreatic necrosis, intensive care unit admissions, requirement for operative intervention, and mortality. Relative risk and associated confidence intervals were calculated by pooling data from the studies investigating each outcome for each comparison. The grading process is done with randomized studies starting as high quality and observational studies starting as low quality. Evidence can then be graded down if there are concerns about the risk of bias, imprecision, indirectness, inconsistency, or evidence of publication bias. Evidence can be graded up if it shows a large effect, plausible confounders that would reduce effect or a dose-response gradient.[17] Randomized and observational studies had to be separated in this process, meaning that in the Grading of Recommendations Assessment, Development and Evaluation tables, some outcomes are listed twice, indicating that both observational and randomized studies investigated this outcome.

RESULTS

The initial search of the databases yielded a total of 410 articles (Fig. 1). Thirteen of these articles met the inclusion criteria, and another 2 articles were identified from reference lists of relevant studies, reviews, and guidelines. A total of 15 studies were therefore included in this systematic review (4 randomized controlled trials, 3 prospective cohort studies, 4 retrospective cohort studies, 1 prospective case-control study, and 3 case series) (Table 1). In total, these 15 studies had 1722 participants (randomized clinical trial = 272, prospective cohort = 343, retrospective cohort = 563, prospective case-control = 129, and case series = 415).

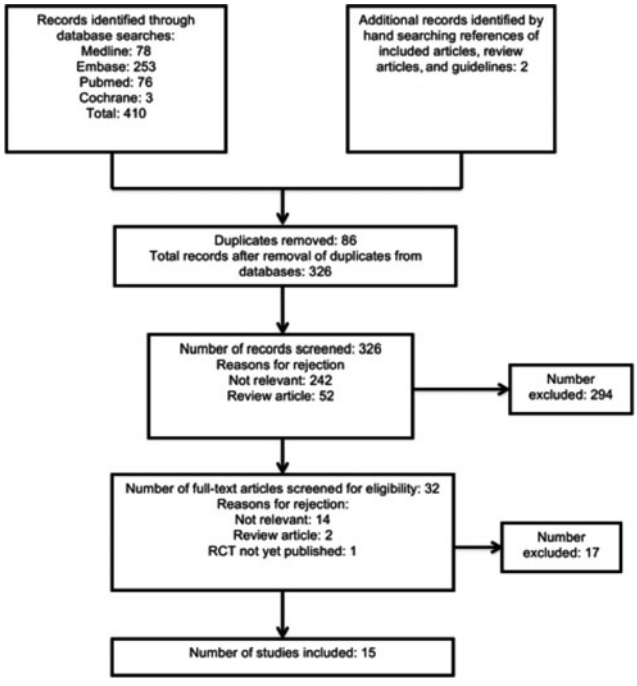

FIGURE 1. Prospect diagram.

Type of Fluids

Only 2 studies specifically investigated the effect of different fluid types on outcomes in AP (Table 1). Du et al[20] compared patients who received Ringer lactate alone versus Ringer lactate with hydroxyethyl starch. Patients receiving the latter showed a reduced mean peak intra-abdominal pressure (mean ± standard deviation, 15 ± 3 cm dihydrogen monoxide vs 17 ± 5 cm dihydrogen monoxide) and significantly lower intra-abdominal pressure on days 2 to 7 ($P < 0.05$). Consequently, by day 5, no patient in the hydroxyethyl starch group still had intra-abdominal hypertension, whereas 33% (7/21) patients in the Ringer lactate group did. However, this study reported no significant differences for the following clinical outcomes: organ failure, length of hospital stay, and in-hospital mortality. Another study by Wu et al[21] showed that patients resuscitated with Ringer lactate showed a reduction of 84% in systemic inflammation from baseline (6/19 down to 1/19; $P = 0.035$) whereas there was no such reduction in the normal saline comparison group. Levels of C-reactive protein were also reduced in the Ringer lactate group (51 mg/dL vs 104 mg/dL; $P = 0.02$). Again, this study showed no significant difference between treatment groups for the following clinical outcomes: intensive care unit transfers, pancreatic necrosis, pancreatic infection, organ failure, length of hospital stay, and mortality.

Rate and Volume of Fluid Administration

Nine studies reported on the effect of the rate of fluid administration on outcomes in AP (Table 1). The median volume given in the first 24 hours in the aggressive treatment groups was 4.5 L (range, 3.5–5.4 L), whereas the median volume given in the first 24 hours in the nonaggressive groups was 3.5 L (range, 1.7–4.0 L). Four of these studies (observational) provide evidence in favor of aggressive fluid resuscitation.[22–25] For example, Brown et al[22] concluded that although fluid resuscitation was not shown to prevent pancreatic necrosis, all patients with a persistent hemoconcentration beyond 24 hours went on to develop pancreatic necrosis. Other studies reported that patients who received less that one third of the total 72-hour fluid volume in the initial 24 hours of treatment experienced higher rates of systemic inflammation, organ failure, and mortality.[23,25] However, in stark contrast to these 4 studies, more recently published studies (both observational and randomized trials) provide evidence for nonaggressive fluid resuscitation.[7–11] These studies have shown an association between aggressive fluid resuscitation and increased organ failure, acute peripancreatic fluid collections renal insufficiency, respiratory insufficiency, intensive care unit admissions, mortality, abdominal compartment syndrome, sepsis, and Acute Physiology and Chronic Health Evaluation II score at days 1, 2, and 3 and volume of fluid sequestration (Table 1).

Resuscitation Goals

A total of 6 studies investigated the use of specific goals about FT in AP[9,21,22,26–28] (Table 1). The goals investigated by these studies included blood urea nitrogen, central venous pressure, hematocrit, heart rate, blood pressure, and urine output. The study by Wu et al[21] investigated whether goal-directed FT based on normalization of blood urea nitrogen would improve patient outcomes. They reached the conclusion that goal-directed FT did not offer any advantage with respect to the outcomes of systemic inflammation and the C-reactive protein level. Central venous pressure was shown to be an inadequate goal for resuscitation in a study concluding that using central venous pressure alone to gauge fluid status may lead to the inappropriate use of inotropes/vasopressors in patients who have been inadequately resuscitated.[27] Controversy surrounds the usefulness of the hematocrit level as a goal. Only 2 studies independently investigated the use of the hematocrit level as a goal of resuscitation

TABLE 1. Studies Summary

Authors	Study Design	Single Center or Multicenter	OCEBM Level	N	Endpoints	Type of Fluid(s)	Rate of Administration	Resuscitation Goal
Du et al[20]	RCT	Single	2	41	Peak IAP	HES, RL	Determined by goal	Hemodynamic stability
De-Madaria et al[7]	PC	Single	3	247	Organ failure >48 h	NS + 5%–10% dextrose	Aggressive: >4.1 L in the first 24 h Moderate: 3.1-4.1 L in the first 24 h Nonaggressive: <3.1 L in the first 24 h	Physician judgment
Wu et al[21]	RCT	Multi	2	40	SIRS	RL or NS	Initial 20 mL/kg bolus + 3 mL/kg per hour and then goal-directed or by physicians judgment	BUN or physician judgment
Warndorf et al[25]	RC	Single	3	434	SIRS, organ failure, mortality	NS (in 85% of cases)	Aggressive: >1/3 of total fluids in the first 24 h Nonaggressive: <1/3 of total fluids on the first 24 h	Not specified
Wall et al[24]	CS	Single	4	286	PNec, mortality	Not specified	1998 (Nonaggressive): 188 mL/h in the first 12 h 2008 (Aggressive): 221 mL/h in the first 12 h	Not specified
Mole et al[27]	CS	Single	4	30	Volume of fluids received	NS, 5%–50% dextrose, Hartmann's, $NaHCO_3$ (1.26%), phosphate, Gelofusine (succinylated gelatin solution), albumin, blood products	Not specified	Physician judgment
Mao et al[9]	RCT*	Single	2	115	Sepsis, mortality	NS, RL, plasma, HES (colloid/crystalloid = 1:2)	Aggressive: goal Hct <0.35 (10.6 L) Nonaggressive: goal Hct ≥0.35 (8.7 L) in the initial 48 h	Hct
Muddana et al[44]	PCC	Single	3	129	PNec	Not specified	4.3 L in the first 24 h and then 3.9 L in the next 24 h	Not specified
Gardner et al[23]	RC	Single	3	45	Mortality, persistent organ failure, duration of hospital stay	NS, RL, or dextrose	Aggressive: >1/3 of total fluids in the first 24 h Nonaggressive: <1/3 of total fluids on the first 24 h	Not specified
Mao et al[10]	RCT	Single	2	76	Mortality, sepsis	NS, RL, plasma, HES	Aggressive: 10–15 mL/kg per hour Nonaggressive: 5–10 mL/kg per hour	HR, CVP, BP, UO
Reddy et al[28]	RC	Single	3	45	Mortality, length of hospital stay	5% dextrose + 0.5 NS	200 mL/h	HR, BP, UO, Hct
Mao et al[11]	PC	Single	3	83	Mortality	NS, RL, plasma, HES	Aggressive: volume expansion standard achieved in the first 24 h Moderate: 25–48 h Nonaggressive: 49–72 h	HR, BP, UO, Hct
Eckerwall et al[8]	CS	Single	4	99	ICU admission, mortality	Crystalloid (unspecified), colloid (albumin)	Aggressive: >4 L Nonaggressive: <4 L in the first 24 h	Spo_2, HR, BP, UO, electrolyte balance
Brown et al[22]	RC	Single	3	39	PNec, Hct	Not specified	Not specified	Hct
Klar et al[26]	PC	Single	3	13	Mortality, PNec	Dextran 60 + Ringer's lactate	Not specified	CVP, Hct

*Randomization was done in a pseudorandom manner where allocation to treatment group was done according to patient age being an odd or even number.

BP indicates blood pressure; BUN, blood urea nitrogen; CS, case series; CVP, central venous pressure; Hct, hematocrit; HES, hydroxyethyl starch; HR, heart rate; IAP, intra-abdominal pressure; n, number of participants; NS, normal saline; OCEBM, Oxford Centre for Evidence-Based Medicine; PC, prospective cohort; PCC, prospective case-control; PNec, pancreatic necrosis; RL, Ringer's lactate; RCT, randomized clinical trial; RC, retrospective cohort; SIRS, systemic inflammatory response syndrome; Spo_2, arterial oxygen saturation; UO, urine output.

in AP.[9,22] One of the studies identified it as a marker that correlates with the development of pancreatic necrosis.[22] In a sample of 39 patients with AP (28 with pancreatic necrosis), all 12 patients with hematocrit levels of 44% or more, which failed to lower within 24 hours, went on to develop pancreatic necrosis, whereas all of the 11 patients with only interstitial AP had reduced hematocrit levels at 24 hours ($P = 0.009$). However, in a more recent study, if a set goal of a hematocrit level of less than 35% was achieved rapidly, it was associated with increased incidence of sepsis (78.6% vs 57.6%; $P = 0.016$) and mortality (43.9% vs 15.3%; $P < 0.05$) when compared with slow hemodilution.[9] A study by Reddy et al,[28] using a protocol-based approach centered around heart rate, blood pressure, urinary output, and hematocrit level, was associated with less severe pancreatitis (crude odds ratio = 11.2; 95% confidence interval = 1.9–68.7; $P = 0.02$), shorter length of hospital stay (median value 7 days vs 3 days; $P = 0.01$), reduced requirement of computed tomographic imaging studies (100% vs 15.6%; $P < 0.001$), and reduced use of antibiotics (50% vs 3.1%; $P = 0.01$).

Grading of the Evidence

The quality of evidence ranges from very low to moderate (Tables 2 and 3). Evidence relating to the different types of fluid was derived from only 2 studies; however, grading the quality of this body of evidence was not appropriate because of the different fluids compared in each study (Ringer lactate vs Ringer lactate + hydroxyethyl starch and normal saline vs Ringer lactate).

The rate of fluid administration is the most investigated aspect of FT in AP (Table 2). Despite this, only moderate-quality evidence was achieved for the 2 conclusions of nonaggressive FT use resulting in lower organ dysfunction (risk ratio = 0.69, 95% confidence interval = 0.54–0.88) and mortality (risk ratio = 0.40, 95% confidence interval = 0.22–0.72) when compared with aggressive fluid resuscitation. As per the Grading of Recommendations Assessment, Development and Evaluation guidelines,[29–38] the randomized clinical trials had to be scored down to a moderate level of evidence because they were not blinded studies and in 1 instance, pseudorandomized allocation was used.[9] The conclusions reached by the observational studies investigating the rate of fluid administration have been contradictory and therefore had to be scored down very low because of inconsistency.

The evidence for goal-directed FT is sparse (Table 3), and the occurrence of specified outcomes were often low due to the small number of participants. As a result, it was not possible to grade the evidence of all of the specified outcomes. Regardless of this, the outcomes that could be graded were scored down to low or very low as a result of being nonblinded and because of the low number of occurrences.

DISCUSSION

This systematic review of FT in AP highlights the surprising paucity of evidence and consensus to guide clinical practice. It also provides the first critical evaluation of the quality of the evidence using a validated grading system (Grading of Recommendations Assessment, Development and Evaluation)[13] and finds that the evidence is predominantly of low to very low quality.

These findings are important because AP is a common cause of acute abdominal pain[39] that carries a high mortality when severe or critical.[2,40–43] FT is universally considered to be the cornerstone of the early management of AP and is considered important in reducing the risks of local and systemic complications and mortality.[5] The inescapable fact is that this review demonstrates that clinicians do not have sufficient quality evidence to know which type of fluid to give, at what infusion rate, and what should be used to guide FT.

The first decision in commencing FT is to decide what fluid to give. Surprisingly, there are only 2 studies comparing the use of alternate fluids and they compared different types.[20,21] The study by Du et al[20] found that resuscitation with Ringer lactate + hydroxyethyl starch resulted in lower rates of intra-abdominal hypertension and the requirement for mechanical ventilation when compared to with resuscitation with Ringer lactate alone. The study by Wu et al[21] found that resuscitation with Ringer lactate reduced systemic inflammation when compared with resuscitation with normal saline. Although these 2 studies did not show a significant difference between treatment groups in the clinical outcomes of organ failure, intensive care unit transfer, pancreatic necrosis, pancreatic infection, length of hospital stay, and in-hospital mortality, they have demonstrated that the type of fluid can influence various inflammatory parameters. In the absence of high-quality evidence in favor of a particular fluid (crystalloid and/or colloid), it is clear that further studies are required.

The second decision is regarding how fast to administer the fluid. Here, there are more studies available to guide the clinician, but the evidence lacks conformity.[7–11,22–25,44] The observational studies are divided; 3 studies[7,8,11] support nonaggressive resuscitation and 4 studies[22–25] support an aggressive approach. The randomized studies to date, however, provide evidence in favor of a nonaggressive approach.[9,10] It is worth noting that despite its common acceptance, the actual evidence to support an aggressive approach to FT is based entirely on inconsistent observational studies.

The third decision is about what to use to guide FT. Here, there are several studies supporting a range of resuscitation goals, from basic bedside assessments to laboratory-based tests,[45] but there is no clear consensus on which is best. The use of bedside assessment of heart rate, blood pressure, and urine output as goals of fluid responsiveness has been shown to be beneficial in a goal-directed FT protocol.[28] In the study by Wu et al,[21] blood urea nitrogen was investigated as a goal for guiding FT in AP. The responsiveness to FT was determined by whether or not the patients' blood urea nitrogen changed, in either direction. This study concluded that a goal-directed fluid resuscitation protocol based on blood urea nitrogen offered no significant benefit. In other studies, lowering the hematocrit level has been promoted as an important goal because of the association between hemoconcentration and pancreatic necrosis.[9,22,26,46–50] Initial research found that a hematocrit level of more than 47%, or the inability to reduce the admission hematocrit level with FT, was a strong risk factor for developing pancreatic necrosis.[46] Follow-up studies have shown that although the admission hematocrit level has a negative predictive value of 88% to 97%, its sensitivity is only 53% to 74% for developing pancreatic necrosis.[44,47–50] Furthermore, Mao et al[9] demonstrated that a goal hematocrit level of less than 35%, if achieved rapidly, increases the incidence of sepsis within 28 days (78.6% vs 57.6%; $P = 0.016$) and in-hospital mortality (43.9% vs 15.3%; $P < 0.05$). This suggests that the hematocrit level has some value but that it cannot be used as a sole marker of adequate fluid resuscitation.

Clinical practice guidelines rely on the synthesis of the best available evidence, and there is a surfeit of guidelines for managing AP. In the review by Loveday et al,[6] 30 guidelines were analyzed and the quality was found to be highly variable. Within these guidelines, the recommendations relating to FT were found to be scarce, with some offering no advice at all.[51–54] There is general consensus that the management of AP by prompt aggressive FT is of critical importance.[51,53,55–57] For the type of fluid, crystalloid is recommended over colloid in just 2 of 7 major international guidelines.[55,57] The specific crystalloids recommended were Ringer lactate and/or normal saline.[57] Neither of the 2 guidelines referenced a study as the basis for these recommendations and are thus graded as expert opinion (level 5). One set of guidelines[56] recommends crystalloid or colloid as required, whereas the remaining 5 guidelines reviewed did not make any mention of fluid selection.[51–54]

TABLE 2. Summary of Findings Table for Nonaggressive Versus Aggressive Fluid Resuscitation

Outcomes	Illustrative Comparative Risks (95% CI)		Relative Effect (95% CI)	No Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Aggressive Fluid Resuscitation	Nonaggressive Fluid Resuscitation				
SIRS (from observational studies) Two or more of the following criteria: heart rate >90 bpm; respiratory rate >20 bpm; $Paco_2$ <35 mm Hg; temperature >100.4 or <96.8; white blood cell count >12,000 or <4000 cells/mm^3	174/1000	52/1000 (35–80)	RR 0.30 (0.20–0.46)	479 (2 studies)	⊕⊕⊖⊖ low	
Organ dysfunction (persistent or new) (from randomized studies) Requiring support	944/1000	650/1000 (511–827)	RR 0.69 (0.54–0.88)	76 (1 study)	⊕⊕⊕⊖ moderate*	
Organ dysfunction (persistent or new) (from observational studies) Requiring support or measures outside of normal range	92/1000	189/1000 (137–262)	RR 2.0 (1.5–2.8)	986 (5 studies)	⊕⊖⊖⊖ very low†	
Pancreatic necrosis (computed tomography) (from observational studies)	147/1000	167/1000 (108–259)	RR 1.1 (0.74–1.8)	454 (3 studies)	⊕⊖⊖⊖ very low†	
ICU admission (from observational studies) Medical records	94/1000	180/1000 (114-284)	RR 1.9 (1.2–3.0)	533 (2 studies)	⊕⊖⊖⊖ very low†	
Operative intervention (from observational studies)	139/1000	132/1000 (78–221)	RR 0.95 (0.56–1.6)	379 (3 studies)	⊕⊖⊖⊖ very low†	
Mortality (from randomized studies) Medical records	326/1000	131/1000 (73–89)	RR 0.40 (0.22–0.72)	191 (2 studies)	⊕⊕⊕⊖ moderate*‡	
Mortality (from observational studies) Medical records	53/1000	99/1000 (62–157)	RR 1.9 (1.2–3.0)	937 (5 studies)	⊕⊖⊖⊖ very low†	

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality, we are very uncertain about the estimate.

*Blinding not specified.

†Nonaggressive fluid resuscitation is shown to increase incidence of outcome in some studies and decrease incidence of outcome in others.

‡Randomization was done in a pseudorandom manner in one study where allocation to treatment group was done according to patient age being an odd or even number.

CI indicates confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; Comparison, aggressive fluid resuscitation; Intervention, nonaggressive fluid resuscitation; Patient or Population, patients with AP; RR, risk ratio; Settings, AP; SIRS, systemic inflammatory response syndrome.

For the rate of fluid administration, only the Japanese guideline[52] warned of the potential dangers of aggressive resuscitation citing the results of the randomized clinical trial conducted by Mao et al.[10] There was only 1 guideline (World Congress of Gastroenterology) that offered specific guidelines with respect to the rate of fluid administration, whereas others merely advised an aggressive approach.[57] The World Congress of Gastroenterology guidelines recommend a rapid initial crystalloid infusion to correct initial deficit within the first few hours of presentation guided by vital signs, oxygen saturation, and urine output. Then the recommendation is for 35 mL/kg per day, plus any extra required to account for ongoing third-space losses. This recommendation is presumably based on expert opinion, as there was no reference made to any published study. Other guidelines recommending nonspecific aggressive resuscitation[51,53,55,56] were based on evidence ranging either from nonblinded randomized clinical trials to animal studies or none at all.

Five of the 7 major international guidelines advise the use of resuscitation goals to guide the rate of FT and when to cease fluid resuscitation.[51,52,55–57] These goals included mean arterial pressure, heart rate, hematocrit level, urinary output, central venous pressure, jugular venous pressure, pulmonary artery wedge pressure, and blood gas and electrolyte parameters. For these goals, targets were provided only for mean arterial pressure (>65 mm Hg)[52] and urinary output (>0.5–1 mL/kg per hour).[52,55,56] These proposed targets of resuscitation were again not referenced to any study. Some guidelines also recommend the hematocrit level[51,52] as a goal to help guide FT. As discussed earlier, there is controversy surrounding the use of hematocrit levels and accordingly their recommendation was that the hematocrit level be used in conjunction with traditional measures of urinary output, heart rate, and blood pressure. An accepted limitation of this type of review is the subjective nature of the Grading of Recommendations Assessment, Development and Evaluation guidelines for scoring the quality of evidence. Recognizing this, the Grading of Recommendations Assessment, Development and Evaluation Working Group published a series of articles to improve standardization of the grading process.[29–38] We adhered closely to the recommendations of the Grading of Recommendations Assessment, Development and Evaluation Working Group in an attempt to mitigate any subjectivity and each study was graded independently by at least 2 authors. Another limitation of this review stems from the inherent variability in the severity of AP included in the different studies. While 6 studies included only severe AP,[9–11,20,23,26] 9 studies included all patients within a range of AP severity.[7,8,21,22,24,25,27,28,44] Furthermore, even the group of patients with severe AP was not homogeneous, as various

TABLE 3. Summary of Findings Table for Goal-Directed Versus Non–Goal-Directed FT

Outcomes	Illustrative Comparative Risks (95% CI)		Relative Effect (95% CI)	No Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Non–Goal-Directed Fluid Therapy	Goal-Directed Fluid Therapy				
SIRS*—not reported	See comment	See comment	Not estimable*	—	See comment	No studies investigating this outcome
Organ dysfunction (persistent or new) (from randomized study)	48/1000	211/1000 (26–1000)	RR 4.4 (0.54–36.2)	40 (1 study)	⊕⊕⊖⊖ low†‡	—
Pancreatic necrosis (computed tomography) (from randomized study)	—§	—§	Not estimable§	40 (1 study)	⊕⊕⊖⊖ low†‡	—
ICU admission (from randomized study)	—§	—§	Not estimable§	40 (1 study)	⊕⊕⊖⊖ low†‡	—
Operative intervention‖—not measured	See comment	See comment	Not estimable‖	—	See comment	No studies investigating this outcome
Mortality (from randomized study)	See comment	See comment	Not estimable§	40 (1 study)	See comment	No occurrences for this outcome
Mortality (from observational study)	48/1000	0/1000 (0–0)	Not estimable§	40 (1 study)	⊕⊖⊖⊖ very low‡¶	

For GRADE Working Group grades of evidence, see Table 2 footnote.
*Only reported as a reduction in prevalence of SIRS.
†Blinding not specified.
‡Very small number of occurrences for this outcome.
§Not estimable as the number of outcomes = 0.
‖No studies investigated this outcome.
¶No occurrences for this outcome.
CI indicates confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; Comparison, non–goal-directed FT; Intervention, goal-directed FT; Patient or Population, patients with AP; RR, risk ratio; Settings, AP; SIRS, systemic inflammatory response syndrome.

definitions of severity were applied. This is a limitation of the available data and could cloud the analysis of the effect of FT on AP patients who are at risk of mortality by including a large number of AP patients with uneventful courses, which would have resolved no matter what therapy was given. One other limitation of this study is the fact that 3 of the 5 primary studies,[9–11] which provided evidence in favor of nonaggressive fluid resuscitation, were from the same group. In particular, we express concern that there is the potential that there may have been patients enrolled in both the 2007 (Ref. 11) and 2009 (Ref. 10) studies simultaneously and there may have been nonconsecutive patients enrolled in the 2009 (Ref. 10) and 2010 (Ref. 9) studies, opening the opportunity for bias.

In conclusion, FT is considered an important early intervention in patients with AP, in theory, offering the opportunity to prevent the severity of the disease and improve clinical outcomes. Given the clinical and economical burden of AP, it is an indictment that, despite decades of research into the management of, there is such a lack of quality evidence to guide the most basic aspects of its FT. Furthermore, what data are available remain conflicted, providing the equipoise necessary for further randomized studies. High-quality randomized data are needed to answer the urgent basic clinical management questions of what fluid to give, at what rate, and how best to guide successful FT delivery in AP.

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