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# Acute Pancreatitis: Need IV Fluid Resuscitation But Avoid a WATERFALL!



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This summary reviews: de-Madaria E, Buxbaum JL, Maisonneuve P, et al. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med 2022;387(11):989-1000. http://www.doi.org/10.1056/NEJMoa2202884.

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## STRUCTURED ABSTRACT

**Question:** What degree of intravenous (IV) fluid hydration leads to optimal outcomes in acute pancreatitis?

**Design:** Multi-center, prospective randomized control trial (RCT), entitled the WATERFALL study (the Early Weight-Based Aggressive vs Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis).

**Setting:** Eighteen centers across 4 countries: India, Italy, Mexico, and Spain.

**Patients**: Adults at least 18 years of age who met clinical criteria of acute pancreatitis (Revised Atlanta Classification: meeting 2 of the following 3: classical abdominal pain, serum amylase or lipase level higher than 3 times the upper limit of the normal, or signs of acute pancreatitis on imaging) were screened for enrollment. The trial only included patients

who received a diagnosis of acute pancreatitis within 8 hours prior to screening and had presented to the emergency room within 24 hours of pain onset. Those with severe disease at baseline, including respiratory, heart, or kidney failure, chronic pancreatitis, or other severe comorbidities including uncontrolled arterial hypertension, hypernatremia, hyponatremia, hyperkalemia, hypercalcemia, decompensated cirrhosis, or low life expectancy were excluded. Patients provided informed consent to participate in the trial.

**Interventions:** Patients were randomly assigned (in a 1:1 ratio) to receive aggressive fluid resuscitation or moderate fluid resuscitation with lactated Ringer's solution. The groups are depicted in **Table 1**. In both groups, investigators performed an initial physical assessment at 0 hours to evaluate for fluid overload, and additional assessments at 3, 12, 24, 48, and 72 hours. As such, hydration was decreased or stopped if there was suspicion of fluid overload in both groups. Oral feeding was started at 12 hours if there was a lower degree of abdominal pain. Fluid resuscitation was stopped once a patient was tolerating oral feeding for 4 hours.

**Outcomes**: Primary outcome was the development of moderately severe or severe acute pancreatitis during hospitalization, defined as meeting at least 1 of the following criteria: local complications, exacerbation of a pre-existing coexisting condition, a creatinine level of at least 1.9 mg per deciliter (170 μmol per liter), a systolic blood pressure of less than 90 mm Hg despite fluid resuscitation, and a ratio of the partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of no more than 300. Multiple secondary outcomes were assessed, including organ failure, intensive care unit admission, infected necrotizing pancreatitis, persistent symptoms, and need for nutritional support, among others. The main safety outcome was fluid overload and required meeting at least 2 of the following 3 criteria: symptoms, physical signs, and imaging evidence of hypervolemia.

**Data Analysis**: The primary outcome, development of moderately severe or severe acute pancreatitis, was evaluated for superiority with an intention-to-treat analysis. There were 3 *a priori* stopping rules: (1) a between-group difference in the primary outcome with a 2-sided *P* value of less than 0.0002 at interim analysis or of less than 0.012 at the second interim analysis; (2) clear evidence of harm in 1 trial group over the other (safety) by the data and safety monitoring board; and (3) a slow recruitment rate.

**Results:** Two hundred forty-nine patients were randomized: 122 patients to the aggressive resuscitation group and 117 patients to the moderate resuscitation group. There were no significant differences between the groups regarding age, sex, gallstones as ideology of the pancreatitis, body mass index, comorbidities and severity, baseline abdominal pain severity, pancreatitis severity, lab markers, respiratory status, or hypovolemic status.
There was no significant difference in the development of the primary outcome, moderately severe or severe acute pancreatitis, which occurred in 22.1% of the aggressive resuscitation group and 17.3% of those in a moderate resuscitation group. Most importantly, aggressive fluid resuscitation was associated with a significantly higher incidence of fluid overload: 20.5% vs 6.3% (adjusted relative risk, 2.85; 95% confidence interval [CI], 1.36 to 5.94). Accordingly, the data and safety monitoring board halted the trial owing to significantly worse results with respect to safety outcomes, and the lack of trend toward improved outcomes. The notable findings are summarized in **Table 2.** Given that the trial was halted, subgroup analyses were limited but fluid overload was also noted in the subgroups of patients with or without systemic inflammatory response syndrome and those with hypovolemia.

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**Table 1: Fluid Resuscitation Strategies**

| | Aggressive fluid resuscitation | Moderate fluid resuscitation |
|---|---|---|
| At 0 hours | Bolus 20 ml/kg, then infusion 3 ml/kg/hr | Infusion 1.5 ml/kg/hr, preceded by bolus 10 ml/kg only if patient has hypovolemia |
| At 3 hours<br>Safety Checkpoint | If there is suspicion of fluid overload, decrease or stop infusion | |
| At 12, 24, 48, and 72 hrs<br>Goal-Directed Therapy Checkpoints | ❖ Hypovolemia<br>- Bolus 20 ml/kg, then infusion 3 ml/kg/hr<br>- Additional boluses of 20 ml/kg if urine output <0.5 ml/kg/hr or SBP <90 mm Hg<br>❖ Normovolemia<br>- Infusion 1.5 ml/kg/hr<br>- Infusion stopped after 48 hr if oral feeding tolerated for >8 hr<br>❖ Suspicion of fluid overload<br>- Decrease or stop infusion<br>- Infusion stopped after 48 hr if oral feeding tolerated for >8 hr | ❖ Hypovolemia<br>- Bolus 10 ml/kg, then infusion 1.5 ml/kg/hr<br>- Additional boluses of 10 ml/kg could be administered in case of urine output <0.5 ml/kg/hr or SBP <90 mm Hg<br>❖ Normovolemia<br>- Infusion 1.5 ml/kg/hr<br>- Infusion stopped after 20 hr if oral feeding tolerated for >8 hr<br>❖ Suspicion of fluid overload:<br>- Decrease or stop infusion<br>- Infusion stopped after 20 hr if oral feeding tolerated for >8 hr |

| Table 2: Outcomes in Each Group | | |
|---|---|---|
| | **Aggressive fluid resuscitation** | **Moderate fluid resuscitation** |
| Moderately severe or severe pancreatitis | 22.1% | 17.3% |
| Fluid overload | 20.5% | 6.3% |
| Total fluid volume administered | 7.8 liters (interquartile range, 6.5 to 9.8) | 5.5 liters (interquartile range, 4.0 to 6.8) |
| Organ failure | 7.4% | 3.9% |
| Persistent organ failure | 6.6% | 1.6% |
| Respiratory failure | 7.4% | 2.4% |
| Necrotizing pancreatitis in 13.9% | 13.9% | 7.1% |
| ICU need | 6.6% | 1.6% |
| Median duration of hospitalization | 6 days (IQR 4-8) | 5 days (IQR 3-7) |

## COMMENTARY

### *Why Is This Important?*

Acute pancreatitis is a vexing problem – there is no clear pharmacologic therapy that has been shown to be of benefit. A standard guideline-recommended intervention is "early aggressive hydration" during the first 12–24 hours.[1] However, the basis of this is theoretical, and the goal is to avoid the intravascular depletion that occurs in pancreatitis, secondary to vomiting, reduced oral intake, third-spacing of fluids, increased respiratory losses, and diaphoresis, with researchers hypothesizing that the third-spacing contributes to pancreatic necrosis and death.[2,3] In fact, studies are conflicting regarding early aggressive hydration in acute pancreatitis, with some showing benefit[4-6] while others show harm.[7,8] Furthermore, not only is it unclear if it is beneficial, but the term "early aggressive hydration" is vague – there is limited clear guidance about how much fluid, when to start, or when to stop. The WATERFALL study is a well-designed and clinically relevant randomized control trial that overcomes methodological issues of prior studies.

### *Key Study Findings*

This well-designed RCT compares moderate and aggressive fluid resuscitation strategies in acute pancreatitis.

There was no significant difference in the incidence of moderately severe or severe pancreatitis between groups (22.1% in the aggressive-resuscitation group and 17.3% in the moderate-resuscitation group; adjusted relative risk, 1.30; 95% CI, 0.78 to 2.18; *P*=0.32), but there were significantly higher rates of fluid overload in the aggressive fluid resuscitation arm: 20.5%, compared to the moderate fluid resuscitation arm: 6.3% (adjusted relative risk, 2.85; 95% CI, 1.36 to 5.94, *P*=0.004).

Therefore, per *a priori* stopping rules,

the trial was halted by the data safety and monitoring board.

### *Caution*

Given the nature of this RCT, there are some methodologic limitations that could not be overcome. First, it is underpowered due to being halted by the data and safety monitoring board. As such, outcomes were unable to be assessed in a statistically sound manner. It was unblinded, which would have been impractical. Lastly, patients in this trial tended to be younger than most acute pancreatitis patients, likely due to the exclusion of patients with heart or kidney failure. Nevertheless, this heightens our caution to avoid overly aggressive fluid resuscitation in patients with acute pancreatitis.

### *My Practice*

This study has made us more cautious about fluid management in acute pancreatitis. Previously, we would monitor volume status. Now, we are even more vigilant, given the clear harm that aggressive fluid resuscitation can entail. Currently, we follow the authors' strategy: an initial fluid rate of 1.5 mL/kg of body weight/hour with boluses only for signs of hypovolemia. We frequently and carefully reassess to avoid volume overload in the first 72 hours with consideration given to diuresis as needed.

A point of interest for us is how this study developed. The first-author, Dr. Enrique de-Madaria, has commented on how a clinical question inspired this paradigm-shifting WATERFALL study – and we are inspired by how a clinical observation regarding a gap in the literature led to such a monumental effort and this multi-center international trial with striking results (https://twitter.com/demadaria/status/1570165278587207680?s=42&t=Wpl242NtG5NaC-1i618fsA).

### *For Future Research*

Since routine aggressive fluid resuscitation can be harmful, we need to identify what moderate resuscitation strategy improves outcomes. This trial only tested 1 moderate-resuscitation strategy. We also need to optimize outcomes for those patients who were excluded from this trial, including those with respiratory, kidney or heart failure at baseline. Lastly, we need pharmacologic therapy: a 17.3% incidence of moderately severe or severe pancreatitis in the moderate-resuscitation group–the arm with "better" outcomes–speaks to how much room for improvement there is.

### *Conflicts of Interest*

Dr. Kumar and Dr. Gardner report no conflicts of interest.

**Note**: The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary.

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