Critical Review Form
Therapy

PGY-2

HYPERLINK "http://pmid.us/36103415"de-Madaria E, Buxbaum JL, Maisonneuve P, et al; ERICA Consortium. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. 2022 Sep 15;387(11):989-1000.

Objectives: **"to investigate the safety and efficacy of aggressive fluid resuscitation as compared with moderate fluid resuscitation in a diverse sample of patients with acute pancreatitis with a range of severity of disease." (p. 990)**

Methods: **This multicenter, international, open label, randomized controlled trial was conducted at 18 centers in four countries (India, Italy, Mexico, and Spain), between May 2020 and September 2021. Consecutive adult patients aged 18 years or older with a diagnosis of acute pancreatitis (defined as at least 2 of the following: typical abdominal pain, serum amylase or lipase > 3 times the upper limits of normal, or signs of acute pancreatitis on imaging) were eligible for inclusion so long as no more than 24 hours had passed since the onset of pain and no more than 8 hours had passed since diagnosis. Exclusion criteria were moderately severe or severe disease (shock, respiratory failure, renal failure), baseline heart failure (NYHA class II or greater), uncontrolled hypertension, hypernatremia, hyponatremia, hyperkalemia, hypercalcemia, estimated life expectancy < 1 year, chronic pancreatitis, chronic renal failure, and decompensated cirrhosis.**

Patients were randomized in a 1:1 ratio to aggressive fluid resuscitation or moderate fluid resuscitation. Aggressive resuscitation involved a bolus of 20 ml/kg of LR over 2 hours, followed by an infusion at a rate of 3 ml/kg/hr. Moderate resuscitation involved an infusion of LR at a rate of 1.5 ml/kg/hr with a bolus of 10 ml/kg over 2 hours only in those with signs of hypovolemia. Physical assessment for signs of volume overload were performed at 3, 12, 24, 48, and 72 hours, with adjustment in resuscitation based on signs of hypovolemia, normovolemia, or volume overload (in which case.

The primary outcome was the development of moderately severe or severe acute pancreatitis during the hospitalization, based on the Revised Atlanta Classification. The main safety outcome was fluid overload. Secondary outcomes included organ failure and local complications during hospitalization, hospital length of stay, ICU admission, days in ICU, use of nutritional support of invasive treatment, presence of SIRS, persistent SIRS (> 48 hours), death, a composite of death/organ failure lasting > 48 hours/infected necrotizing pancreatitis, and symptoms measured using the PAN PROMISE scale.

Out of 676 patients with acute pancreatitis assessed for eligibility, 249 were randomized with 122 in the aggressive resuscitation group and 127 in the moderate resuscitation group. Mean ages were 56 and 57 years, respectively, and 55.7% and

46.5% were female. Patients in the aggressive resuscitation group received a median of 7.8 liters of fluid in the first 48 hours, compared with 5.5 liters in the moderate resuscitation group. Enrollment was stopped early to a difference in the safety outcome observed after 1/3 of the planned enrollment.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion to either receive aggressive fluid resuscitation or moderate fluid resuscitation. "Randomization was stratified according to trial center, the presence or absence of SIRS, and the presence or absence of baseline hypovolemia." (p. 990)
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Patients were randomly assigned in a 1:1 ratio to receive aggressive fluid resuscitation (aggressive-resuscitation group) or moderate fluid resuscitation (moderate-resuscitation group) with the use of a computer-based central randomization system integrated in a Web-based electronic case-report form (REDCap). The random-assignment sequence was concealed from the trial team." (p. 990) This should be more than sufficient to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. There is no mention of crossover between groups and the authors report that, "the trial data were analyzed according to the intention-to-treat principle." (p. 992)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, presence of gallstones, comorbidity score, presence of comorbidities (CAD, diabetes), median PAN-PROMISE score, and baseline labs. The authors do not report baseline lipase levels, proportion of patients with pancreatitis found on imaging, or proportion of patients with recent ethanol use.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. This was an open label study. It is unlikely that performance bias on the part of patients would have influenced outcomes.

2.	Were clinicians aware of group allocation?	Yes. This was an open label study and it is possible that performance bias on the part of clinicians could have influenced outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors.
4.	Was follow-up complete?	Yes. All outcomes were assessed during hospitalization and hence were available for all enrolled patients.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• There was no significant difference in the development of the primary outcome between groups: 22.1% in the aggressive resuscitation group vs. 17.3% in the moderate resuscitation group.
		  ○ adjusted RR 1.30 (95% CI 0.78-2.18).
		• There was also no statistically significant difference in the incidence of organ failure (aRR 1.23, 95% CI 0.47-3.23), local complications (aRR 1.28, 95% CI 0.74-2.22), persistent organ failure (aRR 2.69, 95% CI 0.56-12.88), respiratory failure (aRR 2.19, 95% CI 0.63-7.64).
		• No statistically significant difference was seen in the development of necrotizing pancreatitis, need for ICU admission, hospital length of stay, or PAN-PROMISE scores at various time intervals.
		• Of note, there were potentially clinically significant differences for many of these outcomes, but statistical significance was not achieved due to the small sample size.
		• Aggressive resuscitation was associated with a higher incidence of fluid overload (20.5%) than moderate resuscitation (6.3%): aRR 2.85, 95% CI 1.36-5.94.
		  ○ There was NO difference in the incidence of moderate-to-severe fluid overload (aRR 3.62, 0.37-35.22).

2.	How precise was the estimate of the treatment effect?	See above. This was a small study and hence was underpowered to detect potentially clinically significant differences for many of the outcomes.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Uncertain. This was an international study in which none of the participating sites was in the US. Potentially differences in the underlying etiology of pancreatitis in these countries compared to the US, which were not well described by the authors, could

		potentially impact outcomes. Potential differences in management of pancreatitis in these countries compared to the US could also affect outcomes (external validity).
2.	Were all clinically important outcomes considered?	Yes. The authors considered a vast array of outcomes, including progression to moderately severe or severe pancreatitis, volume overload, organ failure, length of stay, etc.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. The safety outcome for which the study was stopped early is subjectively defined and not necessarily patient-centered. There was no significant difference in the incidence of moderate-to-severe fluid overload or radiographic evidence of pulmonary congestion. As the study was stopped early, after enrollment of only 1/3 of the planned sample size, the study is vastly underpowered to detect potentially clinically significant differences in more patient-centered outcomes. As there was a trend toward an increase in adverse outcomes among patients receiving aggressive resuscitation, it seems reasonable to avoid large volumes of fluid (as given in this group) for patients with mild to moderate pancreatitis.

Limitations:

1. **Despite enrolling at 18 centers over a year and half, only 249 patients were randomized. These results may only apply to a small subset of patients with pancreatitis.**

2. **Despite a planned sample size of 744 patients, only a third of this number was enrolled. By definition, the study was underpowered to detect a difference in the primary outcome.**

3. **The study was stopped early due to a perceived difference in outcomes after only 1/3 of the planned sample size, placing the study at high risk of a type 2 error.**

4. **The primary safety outcome, for which the study was stopped early, was very subjective and not necessarily patient-centered.**

5. **The study was conducted at multiple sites in multiple countries, but none of the sites was in the US (external validity).**

Bottom Line:

This open label, multicenter, randomized controlled trial found no significant difference in adverse outcomes between patients with mild to moderate pancreatitis receiving aggressive vs. moderate fluid resuscitation. The only difference observed

was a higher rate of fluid overload observed with aggressive resuscitation. Of note, the study was stopped early due to this higher rate of fluid overload, with only 1/3 of the planned sample size enrolled. While the study was underpowered to detect a potentially clinically significant difference in any of the outcomes, there was a trend toward increased adverse events in the aggressive resuscitation group.