Critical Review Form
Therapy

PGY-3

HYPERLINK "http://pmid.us/28266591"Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwengela D, Kelly T, Jhun P, Dhanireddy K, Laine L. Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis. Am J Gastroenterol. 2017 May;112(5):797-803.

Objectives: **"to compare aggressive intravenous hydration with standard hydration for the management of acute pancreatitis in a randomized controlled trial." (p. 798)**

Methods: **This randomized controlled trial was conducted in the emergency department at Los Angeles County/University of Southern California Medical Center between April 2013 and November 2015. Patients presenting with acute pancreatitis (defined as at least 2 of the following: epigastric abdominal pain, elevated amylase or lipase > 3 times the upper limits of normal, or signs of acute pancreatitis on imaging) who could be randomized within 4 hours of diagnosis were eligible for inclusion. Exclusion criteria were SIRS, heart failure (NYHA class II or greater), decompensated cirrhosis, hypotension, renal insufficiency (creatinine > 2 mg/dL), need for dialysis, hypoxia (oxygen saturation < 90% on room air), hyponatremia, clinical signs of volume overload, GI bleed, pregnancy, pancreatitis following a procedure, or if pancreatic abscess or necrosis was detected on imaging.**

Patients were randomly assigned in a 1:1 ratio to standard versus aggressive hydration. Aggressive hydration involved a bolus of 20 ml/kg of LR followed by a rate of 3 ml/kg/hr, while those in the standard hydration group received a 10 ml/kg bolus followed by a rate of 1.5 ml/kg/hr. At 12 hours, patients reassessed and had labs drawn; if the hematocrit, BUN, or creatinine level had increased above baseline, patients were then given a 20 ml/kg bolus followed by an infusion of 3 ml/kg/hr regardless of study group. If there was no increase in these lab values, a rate of 1.5 ml/kg/hr was infused or a clear diet was initiated if abdominal pain had decreased. Similar assessments and changes in hydration were made at 24 and 36 hours.

The primary outcome was clinical improvement at 36 hours, defined as a decrease in hematocrit, BUN, and creatinine, decrease in pain level, and tolerance of oral nutrition. Secondary outcomes included rate of clinical improvement, development of SIRS, development of severe pancreatitis, and volume overload.

Out of 198 patients with acute pancreatitis evaluated during the study period, 60 were eligible for inclusion and were randomized (27 to aggressive hydration and 33 to standard hydration). The mean ages were 44.4 years and 45.3 years, respectively and 78% and 73% were male.

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 receive either standard or aggressive resuscitation with LR.
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. "A computer-generated randomization sequence in block sizes of 12 with concealed allocation was used, and patients were blinded to treatment assignment. A total of 72 randomization slots (6 blocks of 12) were provided by a statistician uninvolved in conduct of the study."
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Patients were analyzed in the groups to which they were randomized (intention to treat), regardless of the volume of fluid actually given. Patients in the aggressive resuscitation group received significantly more fluid in the first 24 hours after randomization than the standard resuscitation group (median 5.6 vs. 3.9 liters, $p < 0.001$), but the authors do not report volume given at the patient level.
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, proportion of patients with alcoholic pancreatitis, temperature, pain level, volume of fluid given prior to randomization, and most baseline labs. The authors do not report other baseline vital signs, and while not statistically significant, patients in the aggressive hydration had much higher median lipase levels compared to the standard hydration group (1372 vs. 689 U/L) and were more likely to have elevated white blood cell counts (12% vs. 8% with a WBC > 12 K).
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 the results, particularly given the subjective nature of the outcomes.

3.	Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors (observer bias).
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?	• Patients in the aggressive hydration group were more likely to have clinical improvement within 36 hours compared to patients in the standard resuscitation group (adjusted OR 7.0, 95% CI 1.8-27.8). • Patients in the aggressive hydration group also improved more quickly (HR 1.98, 95% CI 1.05-3.69; aHR 2.32, 95% CI 1.21-4.45). • Patients in the aggressive hydration group were less likely to develop SIRS (aOR 0.14, 95% CI 0.02-0.92), have persistent SIRS (aOR 0.12, 95% CI 0.02-0.94), and develop hemoconcentration (aOR 0.08, 95% CI 0.01-0.49). • One patient in the standard hydration group developed severe pancreatitis and died.
2.	How precise was the estimate of the treatment effect?	See above. This was a very small study and hence the confidence intervals are quite wide.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. This was conducted at a large, urban emergency department in the US. It is likely that patients, physicians, and clinical care were similar to our institution (external validity).
2.	Were all clinically important outcomes considered?	No. The authors did not assess hospital length of stay, ICU admission, patient satisfaction, or need for surgical intervention.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While the study found improved outcomes with aggressive hydration, the study has several key limitations, including very small study size, lack of blinding of clinicians and outcome assessors, and the subjectivity of outcomes. In addition, the primary outcome included changes in laboratory values that are not patient-centered and are of unclear clinical importance. The authors did not consider clinical improvement alone.

Limitations:

1. **The study was very small, including only 60 total patients, with resulting wide confidence intervals and a risk of a type 2 error.**

2. **Both clinicians and outcome assessors were not blinded, raising the risk of performance bias and observer bias.**

3. **The primary outcome was a composite that included changes in laboratory values that are not patient-centered and are of unclear clinical importance.**

Bottom Line:

This small, single-center study found that among patients with mild to moderate acute pancreatitis, those receiving aggressive hydration had a higher rate of improvement within 36 hours based on a composite of lab values, improvement in pain, and tolerance of PO nutrition. The study was limited by small sample size, complete lack of blinding, and a questionable choice of composite outcome.