PROTOCOL NUMBER:		HS-18-00133
TITLE:		**Lactated Ringer's Versus Normal Saline in the Management of Acute Pancreatitis**
STUDY PHASE:		Randomized Trial
STUDY ARMS:		Lactated Ringer's Fluid Therapy, Normal Saline Fluid Therapy
IND OR IDE #:		N/A
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AMENDMENTS/REVISIONS:		

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1.0 BACKGROUND AND HYPOTHESES

Acute pancreatitis is a common problem in the United States necessitating 275,000 hospital admissions per year, with resultant healthcare costs of approximately 2.5 billion USD annually[1]. As numerous trials have failed to show a benefit to specific pharmacologic therapies in acute pancreatitis, the mainstay of treatment has been both supportive care and early, aggressive fluid resuscitation. This practice has been supported by retrospective data[2] and expert opinion[3] and is the core of major society guidelines[1].

We recently conducted and published a randomized controlled trial at LAC+USC comparing aggressive early resuscitation with lactated ringer's (LR) solution (20 mL/kg bolus followed by 3 mL/kg/hr) versus moderate resuscitation with LR (10 mL/kg bolus followed by 1.5 mL/kg/hr) in patients with acute pancreatitis of diverse etiologies (Table 1).[4] We demonstrated that aggressive hydration shortened time to recovery (Figure 1).[4] Aggressive volume resuscitation also reduced the development of SIRS, persistent SIRS, and hemoconcentration (Table 2).[4]. We also did not identify any adverse treatment events associated with this volume of resuscitation[4]. It is theorized that the benefit derived from early, aggressive volume resuscitation is from correcting derangements in the systemic vasculature as well as in the pancreatic microcirculation[5].

Table 1[4]:

Table 1: Characteristics of the study groups

From: Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis

	Aggressive hydration (*N*=27)	Standard hydration (*N*=33)	*P*-value
Demographics			
Age (yrs) (mean (s.d.))	44.4 (13.7)	45.3 (12.3)	0.42
Male (*N* (%))	21 (78)	24 (73)	0.80
Hispanic (*N* (%))	21 (75)	25 (76)	0.89
Alcoholic pancreatitis (*N* (%))	10 (37)	13 (39)	0.90
Comorbidities (*N* (%))	6 (22)	8 (24)	1.0
Clinical presentation			
Temperature (°C) (mean (s.d.))	36.7 (0.3)	36.7 (0.3)	0.90
Initial VAS pain score (0–10 scale) (median (IQR))	8 (2)	8 (3)	0.97
Fluids in emergency room prior to randomization (L) (median (IQR))	1.0 (0.2)	1.1 (1.0)	0.11
Laboratory parameters			
White blood cells >12 × 10^9/l (*N* (%))	12 (44)	8 (24)	0.08
Hematocrit >44% (*N* (%))	12 (44)	12 (36)	0.57
Blood urea nitrogen (mg/dl) (mean (s.d.))	13.6 (4.4)	14.7 (6.2)	0.43
Creatinine (mg/dl) (mean (s.d.))	0.8 (0.2)	0.8 (0.2)	0.85
Albumin (mg/dl) (mean (s.d.))	4.3 (0.4)	4.4 (0.4)	0.15
Calcium (mg/dl) (mean (s.d.))	9.1 (0.4)	9.3 (0.5)	0.14
Lipase (U/l) (median (IQR))	1372 (2195)	689 (4150)	0.30

Figure 1[4]: Clinical Improvement in Pancreaitits in the Aggressive versus Standard Hydration Groups[4]

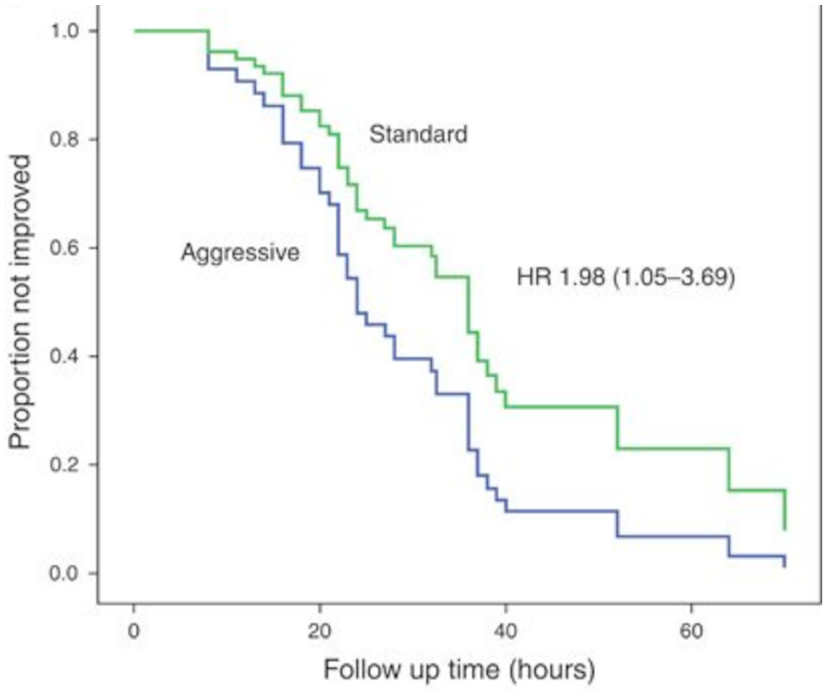

Table 2[4]

Table 2: Secondary outcomes in randomized groups: crude proportions and adjusted odds ratio (logistic regression analysis with covariate of elevated white blood cell count)

From: Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis

	Aggressive hydration (*N*=27)	Standard hydration (*N*=33)	Adjusted odds ratio (95% CI)
Clinical Improvement within 36 h	19 (70%)	14 (42%)	7.0 (1.8–27.8)
Development of SIRS	4 (14.8%)	9 (27.3%)	0.14 (0.02–0.92)
Persistent SIRS	2 (7.4%)	7(21.2%)	0.12 (0.02–0.94)
Development of hemoconcentration	3 (11.1%)	12 (36.4%)	0.08 (0.01–0.49)

CI, confidence interval; SIRS, systemic inflammatory response syndrome.

Our findings validated large cohort studies. This body of work has informed clinical guidelines for actue pancreatitis which recommend aggressive goal directed hydration.[6] Nevertheless, there is significant discussion whether Normal Saline versus Lactated Ringer's solution is the favored type of fluid. While NS has been traditionally used by Internists, advocates of LR suggest its balanced composition may avoid kidney injury and supraphysiologic hyperchloremia.[7] LR also has been proposed at least in theory to have an anti-inflammatory properties.[8].

Nevertheless, small two randomized studies (N=40 patients for both) have shown conflicting results regarding the influence of resuscitation fluid on outcomes in acute pancreatitis. Changes in SIRS prevalence was the outcome in both studies. Wu et al found that LR reduced SIRS prevalence at 24 hours by 84% compared to 0% for NS[9]. Nevertheless, De Madaria et al found no consistent SIRS reduction for LR relative to NS.[10] There was a 31% reduction with LR versus 25% reduction for NS at 48 hours. Given the current state of equipoise the current American Gastroenterology

Association 2018 Acute Pancreatitis Guidelines explicitly state that "The AGA makes no recommendation whether normal saline or Ringer's lactate is used." A larger trial is needed to show whether lR results in a clinically meaningful reduction in SIRS.

2.0 OBJECTIVES AND PURPOSE

To assess the comparative efficacy of normal saline versus lactated ringer's solution in the management of acute pancreatitis.

3.0 STUDY DESIGN

Patients presenting to the Los Angeles County Hospital with acute pancreatitis are the focus population of this study. Pancreatitis will be diagnosed using 2 of 3 criterion; amylase or lipase greater than 3 times the upper limit of normal, classic epigastric abdominal pain, and imaging consistent with acute pancreatitis.

Patients will be randomized to fluid resuscitation with NS or LR within 8 hours of diagnosis of pancreatitis. The inclusion and exclusion criterion will be assessed (see below). Randomization will be performed using a random sequence algorithm with concealed allocation. The amount of fluids and intervention performed in the emergency department prior to randomization will be recorded but not impact randomization strategy.

The patients will be blinded to allocation by covering the bag with an opaque covering. A study physician determining the outcomes (see below) will also be blinded.

Following randomization, the volumes of fluid administered for the resuscitation will be determined by a pre-determined algorithm that will be the same for both treatment arms. As described in the Introduction (Section 1.0) we previously demonstrated in a randomized controlled trial that this volume of intravenous hydration hastens clinical recovery and was not associated with adverse events.[4] The aim of this study is not to study volume but type of fluid used in actue pancreatitis.[4] Thus patients being managed with both intravenous NS and LR will receive the same volume per the algorithm in our prior publication and which is similar to the paradigm used in other trials of fluid therapy in pancreatitis.[4, 11] Our approach to hydration volume and titration also accords with the 2018 recommendations of the American Gastroenterology Association for the management of acute pancreatitis.[6]

The hydration algorithm is as follows: all patients will receive a bolus of the treatment fluid (NS versus LR) at a rate of 5 mL/kg/hour to be administered over the first two hours (total 10 mL/kg) with an assessment for volume overload at 1 hour. They will then receive maintenance fluids at a rate of 3 mL/kg/hour.

After 12 hours participants will have blood urea nitrogen (BUN) assessed, which is part of the standard clinical procedure. Those who do not have a fall in this parameter or who develop SIRS by this 12 hour checkpoint will receive a second 5 mL/kg/hour bolus over two hours (as above) of their designated treatment fluid followed by further treatment fluid at a rate of 3 mL/kg/hour. Those who do have a fall in BUN will receive further treatment fluid at a rate of 3 mL/kg/hour for 12 additional hours. The fluid resuscitation strategy based on the 12 hours checkpoint was utilized in our prior RCT with good safety and efficacy data as well as the prior randomized trial reported by Wu et al.[4, 11]

Patients' volume status will be assessed in the following manner: study physicians will perform a targeted physical exam which will include assessment of JVD, lung auscultation, and monitoring for edema Q12 hours for the first 24 hours, then daily for the remainder of the hospital admission. In elderly patients and those with co-morbidities, the targeted physical exam will be performed Q12 hours for the entire hospital admission. Vitals will also be obtained Q6-8 hours. If they develop signs of fluid overload including pitting edema, ascites, anasacra, pulmonary edema, or dyspnea, or signs of renal failure including oliguria, anuria, or hypotension, they will have their fluid rate managed at the discretion of their treating physicians. However, it will be requested that if further fluid is given that it be the assigned type (LR versus NS).

At 24 hours patients will be assessed for SIRS development (see outcomes). Beyond this point fluid rate will be per the primary team though it still be encouraged that the assigned type of fluid (LR versus NS) is used for additional resuscitation with the rate and volume beyond this point at the discretion of the treating physician. However, if the treating physicians have a strong preference to change to a different fluid type for clinical reasons this will be recorded (for post hoc analysis) and the patient included in the intentiont to treat analysis.[4]

Patients will be recruited until the desired sample size is obtained (see Statistical Considerations), which is expected to occur over 12 months.

4.0 DRUG/DEVICE INFORMATION

Not applicable

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria:

Presentation with acute pancreatitis as defined by two of three criterion; amylase or lipase > 3x the upper limit of normal, classical abdominal pain, or imaging suggestive of pancreatitis. Such radiographic findings include swelling, edema, or heterogeneity of the gland or peripancreatic fluid or stranding.[12]

5.2 Exclusion Criteria

Patients with severe pancreatitis as defined by the Revised Atlanta Classification will be excluded.[13] We are excluding those with severe disease as these patients require highy specified, individualized fluid protocols. Severe pancreatitis is defined by the Revised Atlanta Classification as those with a Modified Marshall score of >2 for their cardiovascular renal, or respiratory system will be excluded (Figure 2).[13] Practically this includes patients with systolic blood pressure <90, serum creatinine >1.9, and PaO2/FiO2 <300 (Figure 3). Since blood gases are unlikely to be drawn on those with mild pancreatitis we will exclude patients with an oxygen saturation <92% on room air and certainly any patients which require intubation for respiratory failure due to pancreatitis.

Figure 2: Modified Marshall Score used for Revised Atlanta Criterion Definition of Severe Pancreatitis (Reference 13)

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal*					
(serum creatinine, μmol/l)	≤134	134–169	170–310	311–439	>439
(serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2
For non-ventilated patients, the FiO_2 can be estimated from below:					
Supplemental oxygen (l/min)	**FiO_2 (%)**				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				

A score of 2 or more in any system defines the presence of organ failure.
*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl.
†Off inotropic support.

Patients who cannot tolerate increased doses of fluids for other reasons will also be excluded. This consists of those with cardiac insufficiency (CI, >NYHA Class II heart failure), pulmonary edema, dialysis requirement, or severe liver dysfunction (albumin < 3mg/dL, known cirrhosis).

Pregnant women will also be excluded as they are prone to retain sodium and water, which puts them at increased risk of pulmonary congestion, ascites or peripheral edema.

Patients who are incarcerated, younger than eighteen, or unable to give informed consent will be excluded.

Individuals who present with clinical signs of edema or anasacra, including pulmonary congestion, peripheral swelling, and ascites, will also be ineligible for the study.

Administration of fluids prior to the enrollment in the study will not be an exclusion criterion as this reflects actual clinical practice (hydration during evaluation period) however all fluids given prior to the study will be meticulously recorded.

5.3 Withdrawal Criteria

5.3.1 Patients who wish to cease participation in the study will be withdrawn from the study.

5.3.2 Patients will also be withdrawn from the study if their treating physicians wish to withdraw them for any reason.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 Stratification factors. Patients will not be stratified prospectively. At the end of the study, subgroup analysis will be performed to compare the results of those with gallstone pancreatitis, alcoholic pancreatitis, post procedure pancreatitis, and pancreatitis due to other origins.

6.2 Descriptive factors. Sex, age, ethnicity, comorbidities, and surgical history will be recorded.

6.3 There will be a randomization of patients to NS versus LR fluids groups in 1:1 allocation ratio. Randomization will be performed by the SC-CTSI Bioinformatics and Bioinformatics Group.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

Not applicable

7.2 Drug studies: Not applicable

Criteria for removal from treatment

7.3.1 Patients who develop a complication of the study, namely fluid overload will be withdrawn from the treatment protocol but not the study, and will have their fluid rates managed by their treating physicians. These patients have met the secondary outcome of fluid overload.

7.3.2 Patients who develop renal failure or severe pancreatitis will also be withdrawn from the treatment protocol but not the study, and their fluid rates will be managed at the discretion of their treating physicians.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Side effects/Toxicities to be monitored.

8.1.1
Fluid overload including pitting edema, ascites, anasacra, pulmonary edema, or dyspnea is the primary side effect of the treatment.

8.1.2
Electrolyte abnormalities, including hyperchloremia, metabolic acidosis, and hyponatremia are potential side effects of the fluids administered.

8.1.3
Long-term toxicities to be monitored after completion of therapy: There are no foreseeable long-term effects of the study fluids.

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8.2 Adverse Event Reporting:

8.3.1 Type of event to be reported and timing of reports.

If patients develop fluid overload including pitting edema, ascites, anasacra, pulmonary edema, or dyspnea they will be removed from the treatment protocol and be managed at the discretion of their treating physicians. This will be reported to the principal investigators and will be reviewed by the study team as well as two staff physicians in the

gastroenterology division who are not part of the study team. This will also be reported to the IRB.

If patients experience any further events that are detected on telephone call follow-up these will be coded as A) related to study or B) not related to the study. Their severity and A) whether they were expected or B) not expected will also be recorded. These complications will also be reported to the principal investigators and will be reviewed by the study team as well as two staff physicians in the gastroenterology division who are not part of the study team. They will also be reported to the IRB.

8.32 Places for submitting reports: IRB, Sponsor, Investigational Drug Branch, etc.

Adverse events will be reported to the IRB and data safety monitoring committee.

8.4 Data Monitoring Committee

The data safety monitoring committee will include the principal investigators from medicine/gastroenterology and surgery as well as the entire study team. An outside senior physician from gastroenterology or surgery will also be asked to participate. Meetings will occur every 3 months.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Parameter	**Admisson**	**12**	**24 hours**	**Daily in hospital**	**Follow up phone call 2 weeks**
Comprehensive History & Complete Physical Examination	X				
Targeted History & Physical Examination		X	X	X	
Targeted History					X
Metabolic panel-part of standard of care for pancreatitis	X	X			

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Endpoint Definitions

Primary Outcome will be the change in SIRS prevalence from enrollment to 24 hours.
SIRS will be defined as 2/4 criterion[14]

a) HR >90
b) RR >20 or paCO2 <32 on room air

c) T >100.4 F <96.8 F
d) WBC >12, <4 or >10%

Secondary Outcomes

1) Change in SIRS prevalence from enrollment to 48 hours and 72 hours.
2) Moderately severe acute pancreatitis will be defined if at least 1 of the criterion is present[16]
   1. Organ failure that resolves within 48h (transient organ failure)
   2. Local or systemic complications without persistent organ failure

3) Severe acute pancreatitis will be defined as persistent organ failure (>48 hrs)[16].
4) Change in PASS Score from enrollment to 24, 48, and 72 hours[17].
5) ICU admission as well as ICU intervention including intubation, respiratory distress without intubation defined as RR>20 AND O2 Sat<90% on room air, death, development of extrapancreatic fluid collection (EPFS) will also be secondary outcomes.
6) Length of hospitalization
7) Persistent pain or disability after discharge as well as time to return to work will be recorded by a 2 week follow up phone call.
8) Time to advancement of oral diet and discharge will also be secondary outcomes.

11.0 SPECIAL INSTRUCTIONS:

Not applicable

12.0 DATA COLLECTION AND MONITORING

SEE ATTACHED INITIAL, INTERVAL, AND TELEPHONE COLLECTION FORM. In collaboration with Southern California Clinical and Translational Science Institute (SC CTSI), a (Research Electronic Data Capture) REDCap database[1] will be developed and utilized for this study. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources[2]. Provision of data to IRB, NIH, and FDA is facilitated by this database system.

13.0 STATISTICAL CONSIDERATIONS

13.1

Descriptive statistics will be performed for each group (LR versus NS) and comparisons made to determine if the groups are balanced by patients' characteristics and various pertinent features such as type of pancreatitis. Intent-to-treat analysis of the primary outcome will be achieved using logistic regression models to assess whether there is a difference in SIRS prevalence at at 24 hours, adjusting for presence of SIRS at baseline. The odds of SIRS in the LR group compared with the NS group will be reported to assess clinical effectiveness of LR versus NS. We will also examine SIRS components independently using this same method. Dichotomous secondary outcomes will use this method, while length of hospitalization and time to advancement of oral diet and discharge

will be analyzed using cox proportional hazard regression models. Analyses will be performed using SPSS (V.24), and *a priori* $\alpha = 0.05$.

As described in the introduction one small RCT showed an 83% greater reduction in SIRS prevalence for LR relative to NS at 24 hours and the other showed no significant reduction.[10-11]

Thus we based our calculation on the known LAC+USC SIRS prevalence for patient s managed with NS (our sampling population) and the decrease in SIRS prevalence which would be defined as clinically significant.[15]

We used G*Power to estimate *a priori* sample size for SIRS estimating a prevalence of SIRS of 50% for NS ($\alpha = 0.05$, two sided; $1-\beta = 0.80$) based on our published large observational cohort of patients with acute pancreaititis at LAC+USC.[15]
Based on discussion with experts we defined a clinically significant reduction of SIRS prevalance of LR of 50% relative to NS. Our proposed sample size of 119 will allow us to detect a clinically significant difference in SIRS prevalence at 24 hours between LR and NS

14.0 REGISTRATION GUIDELINE

14.1 Phone number to register the patients. 323 409 5371

14.2 Forms and records needed for registration: Informed Consent, Registration/Eligibility Worksheet, Flow Sheet, etc.

SEE ATTACHED INITIAL COLLECTION FORM AND INFORMED CONSENT FORM

15.0 BIOHAZARD COMTAINMENT

Not applicable

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

17.0 REFERENCES

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