ORIGINAL ARTICLE

Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis

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Journal Club 26.10.2022

Tabea Pfister

Background

- Moderatly severe or severe disease -> 35% of patients with acute pancreatitis
- Hypovolemia in AP can occur for many reasons, including third-space fluid loss
- Hypoperfusion of the pancreas and hypovolämie-> Necrosis

ORIGINAL CONTRIBUTIONS: PANCREAS AND BILIARY TRACT

Influence of Fluid Therapy on the Prognosis of Acute Pancreatitis: A Prospective Cohort Study

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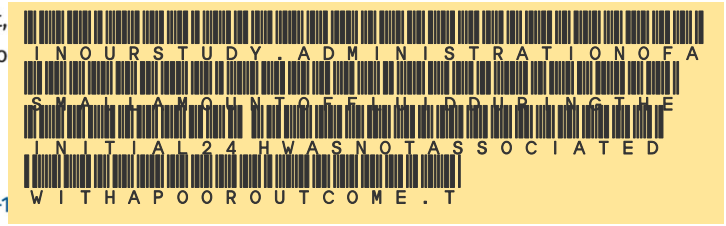
Author Information

American Journal of Gastroenterology: October 2011 - Volume 106 - Issue 10 - p 1843-1
doi: 10.1038/ajg.2011.236



ORIGINAL ARTICLE

Fluid therapy for severe acute pancreatitis in acute response stage

MAO, En-qiang; TANG, Yao-qing; FEI, Jian; QIN, Shuai; WU, Jun; LI, Lei; MIN, Dong; ZHANG, Sheng-dao

Author Information

Chinese Medical Journal: January 2009 - Volume 122 - Issue 2 - p 169-173
doi: 10.3760/cma.i.issn.0366-6999.2009.02.011

CONTROLLEDFLUIDRESUSCITATIONOFFERS
BETTERPROGNOSISINPATIENTSWITHSEVERE
VOLUMEDEFICITWITHIN72HOURSOFSAPONSET

ORIGINAL CONTRIBUTIONS: PANCREAS AND BILIARY TRACT

Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatiti

Buxbaum, James L MD[1]; Quezada, Michael MD[1]; Da, Ben MD[1]; Jani, Niraj M
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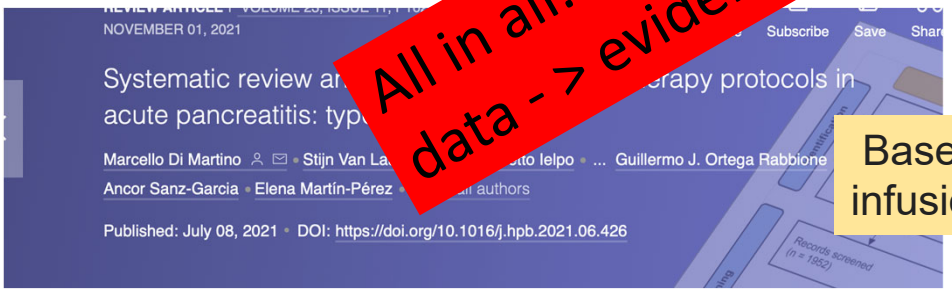
EARLYAGGR OUSHYDRATION
WITHL SOLUTIONHASTENS
PATIENTSWITH
REATITIS

All in all: Limited by heterogenity and qualitiy of data - > evidence for this pratice is limited



Based on low-certainty evidence, moderate-rate fluid infusion should be preferred over high-rate infusion

WATERFALL-Trial

- the Early Weight-Based Aggressive vs. Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis:
- Open-Label Multicenter Randomized Controlled Trial
- Investigation about the safety and efficacy of aggressive fluid resuscitation as compared with moderate fluid resuscitation
- sample of patients with acute pancreatitis with a range of severity of disease

What do the guidlelines say?

Question 1: What is the Role of Intravenous Hydration in the Initial Management of Patients With Acute Pancreatitis?

combinations. In AP, 3 guidelines are instructive. Recommendations were weak[8] or strong[9,39] for lactated Ringer's solution as the preferred type of fluid, with different rates and levels of evidence: 5–10 mL/kg/h[9] (moderate quality evidence), 250–500 mL/h during the first 12–24 hours using frequent clinical assessments to decrease BUN[8] (moderate quality evidence), and 150–600 mL/h[39] (low-quality evidence). One guideline[9] also made weak recom-

American Gastroenterological Association
5-10 ml/kg/h

American College of Gastroenterology
250-500 ml/h during the first 24 h

Japanese Association of Gastroenterology
150-600 ml/H

Vege SS et all. Initial Medical Treatment of Acute Pancreatitis: American Gastroenterological Association Institute Technical Review. Gastroenterology. 2018 Mar

Methods

- multicenter, open-label, parallel-group, randomized, controlled, superiority trial,
- 18 centers across four countries (India, Italy, Mexico and Spain)
- May 2020 – September 2021

- Inclusion-Criteria
  - >18 years of age
  - Diagnosis of acute pancreatitis
  - Pain onset <24 h
  - Diagnosis 8 h before enrollemend

30% (2,11). The revised Atlanta classification requires that two or more of the following criteria be met for the diagnosis of acute pancreatitis: *(a)* abdominal pain suggestive of pancreatitis, *(b)* serum amylase or lipase level greater than three times the upper normal value, or *(c)* characteristic imaging findings (2). Contrast material–enhanced

Foster BR et all. Revised Atlanta Classification for Acute Pancreatitis: A Pictorial Essay. Radiographics. 2016 : Radiographics.

Methods: Exclusion Criteria

Exclusion criteria

A. Uncontrolled arterial hypertension (systolic blood pressure >180 and/or diastolic blood pressure >100 mmHg)
B. New York Heart Association class II heart failure (slight limitation of physical activity; fatigue, palpitations, or dyspnea with ordinal physical activity) or worse, or ejection fraction <50% in the last echocardiography
C. Decompensated cirrhosis (Child's class B or C)
D. Hyper or hyponatremia (<135 or >145 mEq/L)
E. Hyperkalemia (>5 mEq/L)
F. Hypercalcemia (albumin or protein-corrected calcium >10.5 mg/dL)
G. Baseline kidney failure (basal glomerular filtration rate <60 mL/min per 1.73 m^2)
H. Clinical signs or symptoms of volume overload or heart failure at recruitment (dyspnea, peripheral edema, pulmonary rales, or evidently increased jugular ingurgitation at 45º)
I. Shock or respiratory failure according to the revised Atlanta classification at recruitment (non-fluid-responding systolic blood pressure <90 mmHg, PaO_2/FIO_2 ≤300)

4

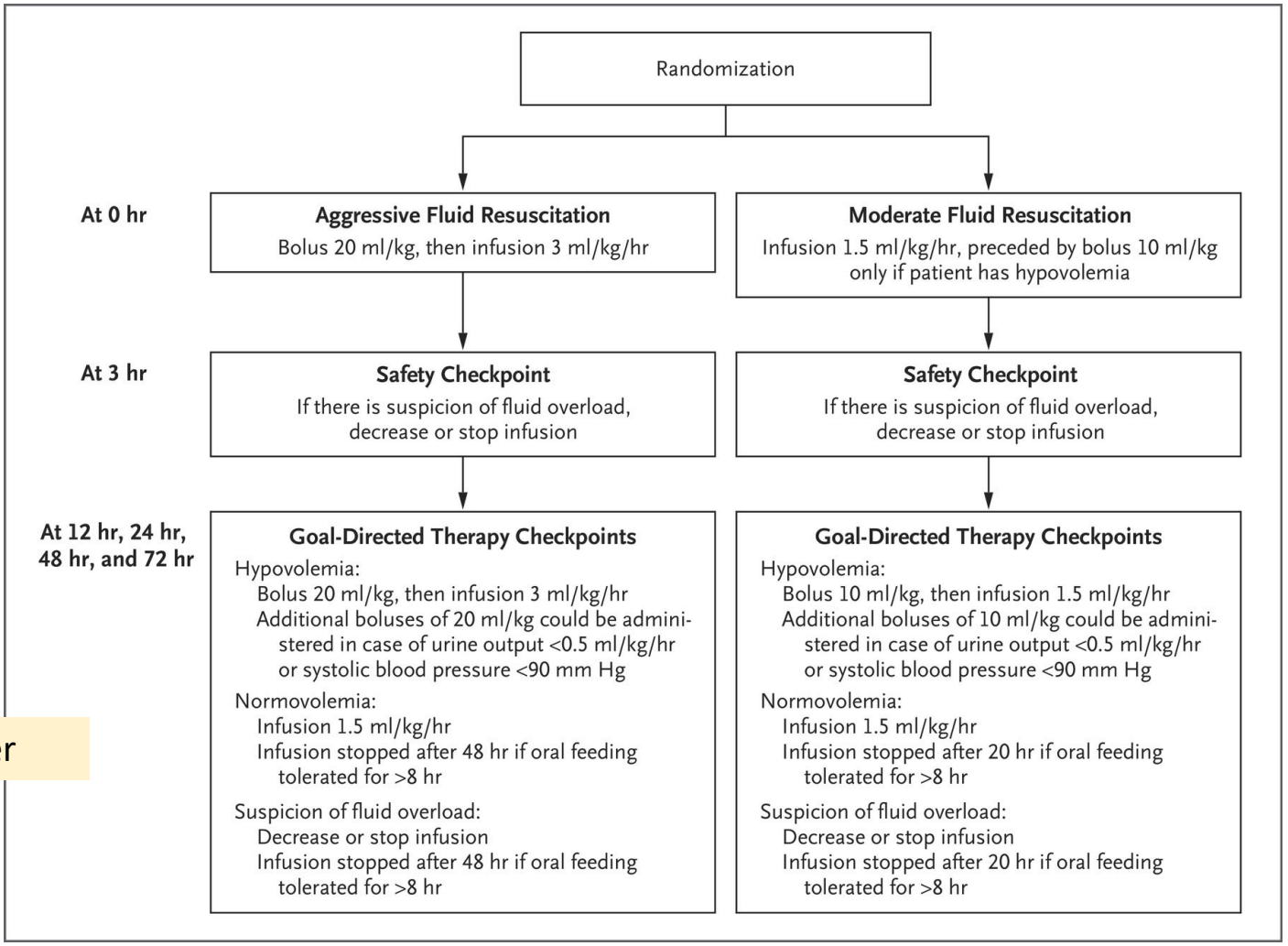
J. Time from pain onset to arrival to emergency room >24 h
K. Time from confirmation of pancreatitis to randomization >8 h
L. Severe comorbidity associated with an estimated life expectancy <1 year

- Positive Criteria for moderately severe or severe disease
- Heart failure
- Uncontrolled hypertension or dyselectriemia
- Chronic disease like Cirrosis, Pancreatitis
- with life expectancy < 1 Jahr

Disease severity	Symptoms
Mild acute pancreatitis	No organ failure No local or systemic complications
Moderately severe acute pancreatitis	Organ failure that resolves within 48 h (transient organ failure) Local or systemic complications without persistent organ failure
Severe acute pancreatitis	Persistent organ failure (>48 h) Single organ failure Multiple organ failure

Methods

Fluid resusitation with Ringer



Outcomes

- Primary outcome
  - Moderately severe or severe pancreatitis

Disease severity	Symptoms
Mild acute pancreatitis	No organ failure No local or systemic complications
Moderately severe acute pancreatitis	Organ failure that resolves within 48 h (transient organ failure) Local or systemic complications without persistent organ failure
Severe acute pancreatitis	Persistent organ failure (>48 h) Single organ failure Multiple organ failure

- Secondary outcome
  - organ failure and local complications

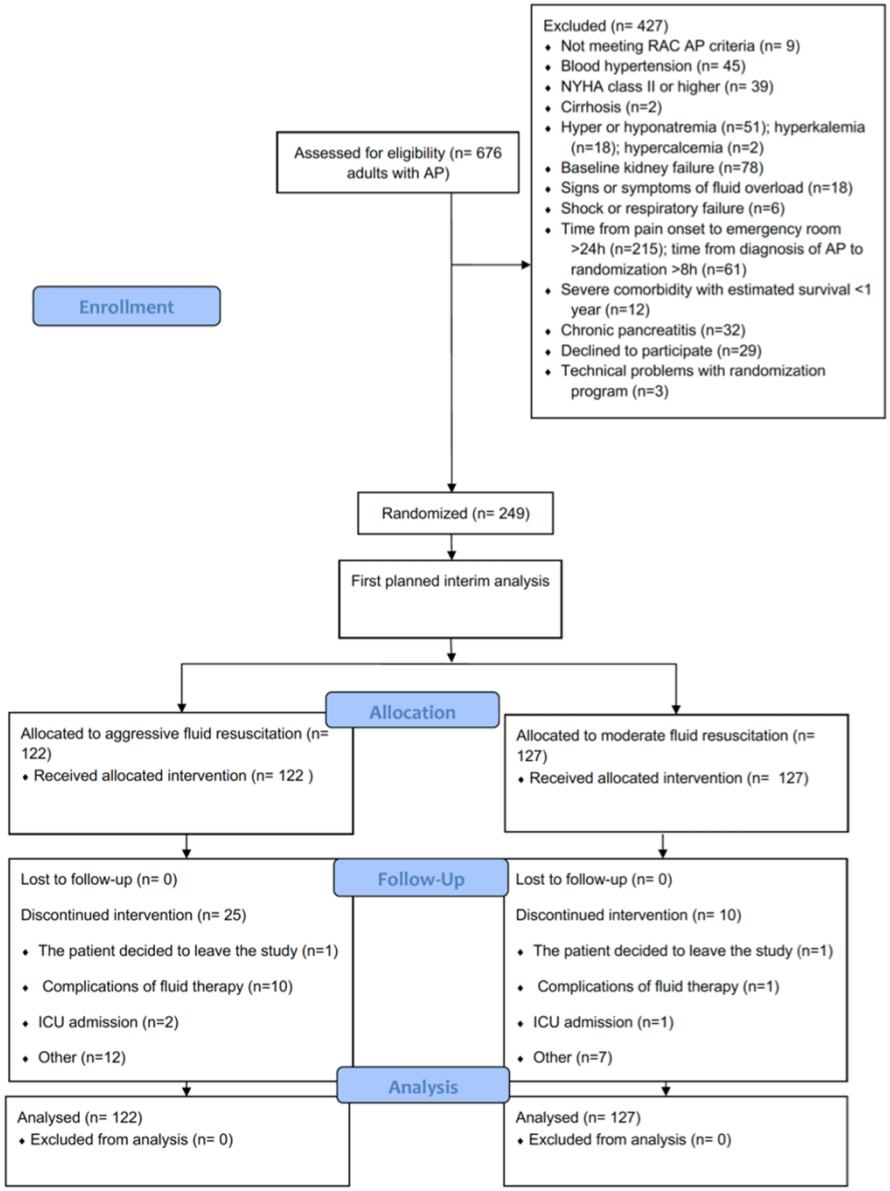
- the duration of hospital stay;
- intensive care unit (ICU) admission;
- the number of days in the ICU;
- the use of nutritional support or invasive treatment after randomization and during the hospitalization; t
- the presence of SIRS
- persistent SIRS (lasting >48 hours within the first 72 hours after randomization)
- C-reactive protein levels in blood at 48 hours and 72 hours
- death; a composite outcome of death,

- Main safety outcome
  - Fluid overload

Statistical analysis

- Anticipated incidence of moderatly severe or severe pancreatitis – 35%
- Sample size of 744 Patients > 80% power to detect a between-group difference
- Two interim analyses were planned (after one third and two third of the patients)

Patients


Assessed for eligibility (n= 676 adults with AP)
Excluded (n= 427)
Not meeting RAC AP criteria (n= 9)
Blood hypertension (n= 45)
NYHA class II or higher (n= 39)
Cirrhosis (n=2)
Hyper or hyponatremia (n=51); hyperkalemia (n=18); hypercalcemia (n=2)
Baseline kidney failure (n=78)
Signs or symptoms of fluid overload (n=18)
Shock or respiratory failure (n=6)
Time from pain onset to emergency room >24h (n=215); time from diagnosis of AP to randomization >8h (n=61)
Severe comorbidity with estimated survival <1 year (n=12)
Chronic pancreatitis (n=32)
Declined to participate (n=29)
Technical problems with randomization program (n=3)
Enrollment
Randomized (n= 249)
First planned interim analysis
Allocation
Allocated to aggressive fluid resuscitation (n= 122)
Received allocated intervention (n= 122)
Allocated to moderate fluid resuscitation (n= 127)
Received allocated intervention (n= 127)
Follow-Up
Lost to follow-up (n= 0)
Discontinued intervention (n= 25)
The patient decided to leave the study (n=1)
Complications of fluid therapy (n=10)
ICU admission (n=2)
Other (n=12)
Lost to follow-up (n= 0)
Discontinued intervention (n= 10)
The patient decided to leave the study (n=1)
Complications of fluid therapy (n=1)
ICU admission (n=1)
Other (n=7)
Analysis
Analysed (n= 122)
Excluded from analysis (n= 0)
Analysed (n= 127)
Excluded from analysis (n= 0)

Patients

7.8 l/48 h

5.5 l/48 h

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Aggressive Fluid Resuscitation (N=122)	Moderate Fluid Resuscitation (N=127)
Age — yr	56±18	57±17
Female sex — no. (%)	68 (55.7)	59 (46.5)
Gallstone cause of pancreatitis — no. (%)	80 (65.6)	71 (55.9)
Median body-mass index (IQR)†	27 (24–31)	27 (25–31)
Median Charlson comorbidity score (IQR)‡	2 (0–3)	2 (0–3)
Coronary artery disease — no. (%)	2 (1.6)	1 (0.8)
Diabetes — no. (%)	18 (14.8)	24 (18.9)
Cancer in previous 5 yr — no. (%)	9 (7.4)	5 (3.9)
Median BISAP score (IQR)§	1 (0–1)	1 (0–1)
Median PAN-PROMISE score (IQR)¶	31 (21–45)	27 (20–40)
Median urea (IQR) — mg/dl	32 (25–41)	36 (27–42)
Median hematocrit (IQR) — %	44 (40–47)	44 (41–46)
Median creatinine (IQR) — mg/dl	0.8 (0.7–0.9)	0.8 (0.7–1.0)
SIRS — no. (%)‖	35 (28.7)	29 (22.8)
Hypovolemia — no. (%)	64 (52.5)	65 (51.2)

Efficacy outcomes

No significant between group difference in the developement of a moderatly severe or severe AP

Primary outcome
22 % vs 17.3%

ICU Admission
8% vs. 2 %

Any organ failure
9% vs. 5%

Hospital stay
6 days vs 5 days

More complications in the aggressive fluid resuscitation group

More invasive treatments in the aggressive fluid resuscitation group

Table 2. Primary and Secondary Outcomes.*

Outcome	Aggressive Fluid Resuscitation (N=122)	Moderate Fluid Resuscitation (N=127)	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)	No. of Patients with Missing Data†
Primary outcome: moderately severe or severe pancreatitis — no. (%)‡	27 (22.1)	22 (17.3)	1.28 (0.77–2.12)	1.30 (0.78–2.18)	0
Severe pancreatitis — no. (%)	8 (6.6)	2 (1.6)	4.16 (0.90–19.22)	2.69 (0.56–12.88)	0
Local complications — no. (%)					
Any complication	25 (20.5)	21 (16.5)	1.24 (0.73–2.09)	1.28 (0.74–2.22)	0
Necrotizing pancreatitis§	17 (13.9)	9 (7.1)	1.97 (0.91–4.24)	1.95 (0.87–4.38)	0
Infected necrotizing pancreatitis	5 (4.1)	3 (2.4)	1.74 (0.42–7.10)	1.45 (0.38–5.49)	0
SIRS — no./total no. (%)					
At 12 hr	27/120 (22.5)	23/126 (18.3)	1.23 (0.75–2.03)	1.11 (0.69–1.78)	3
At 24 hr	22/115 (19.1)	17/125 (13.6)	1.41 (0.79–2.51)	1.34 (0.76–2.39)	9
At 48 hr	18/112 (16.1)	16/119 (13.4)	1.20 (0.64–2.23)	1.15 (0.59–2.23)	18
At 72 hr	9/102 (8.8)	15/105 (14.3)	0.62 (0.28–1.35)	0.82 (0.37–1.83)	42
Persistent SIRS — no./total no. (%)¶	10/96 (10)	7/104 (7)	1.55 (0.61–3.90)	1.32 (0.52–3.38)	49
Other outcomes					
Invasive treatment — no. (%)	11 (9.0)	5 (3.9)	2.29 (0.82–6.40)	1.59 (0.58–4.33)	0
Nutritional support — no. (%)‖	7 (5.7)	5 (3.9)	1.46 (0.48–4.47)	1.19 (0.43–3.27)	0
ICU admission — no. (%)	8 (6.6)	2 (1.6)	4.16 (0.90–19.22)	2.71 (0.64–11.51)	0
Exacerbation of coexisting condition — no. (%)	4 (3.3)	0	9.37 (0.51–172.20)**	NA	0
Any organ failure — no. (%)	9 (7.4)	5 (3.9)	1.87 (0.65–5.43)	1.23 (0.47–3.23)	0
Persistent organ failure — no. (%)††	8 (6.6)	2 (1.6)	4.16 (0.90–19.22)	2.69 (0.56–12.88)	0
Shock — no. (%)	5 (4.1)	1 (0.8)	5.20 (0.62–43.91)	3.58 (0.47–27.56)	0
Respiratory failure — no. (%)	9 (7.4)	3 (2.4)	3.12 (0.87–11.26)	2.19 (0.63–7.64)	0
Kidney failure — no. (%)	4 (3.3)	3 (2.4)	1.39 (0.32–6.07)	1.22 (0.30–5.00)	0
Death — no. (%)	4 (3.3)	1 (0.8)	4.16 (0.47–36.73)	3.05 (0.32–28.76)	0
Death, persistent organ failure, or infected necrotizing pancreatitis — no. (%)	9 (7.4)	4 (3.1)	2.34 (0.74–7.41)	1.60 (0.50–5.10)	0
Median duration of hospital stay (IQR) — days	6 (4–8)	5 (3–7)	1.31 (1.00–1.73)	1.31 (0.98–1.75)	0
Median no. of days in ICU (IQR)‡‡	0 (0–0)	0 (0–0)	NA	NA	0
Median PAN-PROMISE score (IQR)					
At 12 hr	23 (12–35)	18 (10–31)	1.31 (1.02–1.70)	1.24 (0.95–1.61)	4
At 24 hr	17 (6–27)	12 (6–23)	1.28 (1.00–1.65)	1.29 (1.00–1.66)	11
At 48 hr	10 (4–24)	8 (2–18)	1.28 (0.98–1.67)	1.29 (1.01–1.66)	21
At 72 hr	7 (2–18)	5 (2–14)	1.20 (0.90–1.58)	1.20 (0.91–1.58)	45
Median C-reactive protein (IQR) — mg/dl					
At 48 hr	9.8 (1.6–21.9)	8.7 (3.2–19.0)	1.06 (0.81–1.39)	1.09 (0.81–1.48)	39
At 72 hr	8.2 (1.9–21.8)	9.0 (3.3–21.7)	0.96 (0.72–1.28)	0.95 (0.70–1.29)	63

Safety outcomes

Fluid overload
25% vs. 8%

	Aggressive Fluid Resuscitation (N=122)	Moderate Fluid Resuscitation (N=127)	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)	P Value
	number (percent)				
Fluid overload†	25 (20.5)	8 (6.3)	3.25 (1.53–6.93)	2.85 (1.36–5.94)	0.004
Moderate-to-severe fluid overload‡	6 (4.9)	1 (0.8)	6.25 (0.76–51.13)	3.62 (0.37–35.22)	0.23
Symptoms of fluid overload: dyspnea	22 (18.0)	10 (7.9)	2.29 (1.13–4.64)	1.85 (0.95–3.61)	0.08
Signs of fluid overload	32 (26.2)	14 (11.0)	2.38 (1.34–4.24)	2.36 (1.33–4.19)	0.003
Peripheral edema	12 (9.8)	4 (3.1)	3.12 (1.04–9.42)	2.70 (0.90–8.09)	0.07
Pulmonary rales	30 (24.6)	13 (10.2)	2.40 (1.32–4.38)	2.36 (1.30–4.28)	0.004
Increased jugular venous pressure, hepatojugular reflux, or both	5 (4.1)	3 (2.4)	1.74 (0.42–7.10)	1.53 (0.33–7.11)	0.58
Evidence of fluid overload on hemodynamic testing or imaging	13 (10.7)	7 (5.5)	1.93 (0.80–4.68)	1.34 (0.54–3.36)	0.53
Evidence of heart failure on echocardiogram	0	1 (0.8)	0.35 (0.01–8.43)§	NA	0.32
Radiographic evidence of pulmonary congestion	13 (10.7)	7 (5.5)	1.93 (0.80–4.68)	1.34 (0.54–3.36)	0.53
Invasive cardiac catheterization	1 (0.8)	2 (1.6)	0.52 (0.05–5.67)	0.50 (0.05–5.51)	0.56

Time to fluid overload
34 h vs. 46 h

Therapy of Fluid overload:

- Decrased hydratation 12% vs. 0%
- Diuretica 88% vs. 100%
- Inotropica 8% vs 0%
- Intubation: 1 Patient of aggressive Fluid group

Discussion

- Aggressive fluid resuscitation increases the risk of volume overload
  - Increased harm without improvement -> trial was stopped
- Increased risk for Fluid overload
  - Overall population
  - Patient with SIRS at the baseline
  - Patients with hypovolamia
- No significant between-group difference in the risk of moderately severe or severe pancreatitis

Discussion

- Agressive Fluid resuscitation
  - higher intensity of symptoms
  - Longer hospital stay
  - Higher incidence of necrotizing pancreatitis

- Aggressive hydration is linked to worse outcomes in criticall ill patients (?)
- Pancreatitis is associated with a higher intraabdominal pressure -> higher intensity of symptoms when given fluids

Limitations

- Underpowered: The Trial was terminated at the first interim analysis
- Bias due openlabel trial
- Even patients in the moderate-resuscitation group received a liberal volume of fluid -> to aggressive in the aggressive fluid resuscitation group?
- the exclusion of patients at high risk for volume overload -> Selection if patients with less severe disease
- Oral feeding

Remaining Questions

- Only patients with mild pancreatitis – what to do with severe ill patients?
- What is happening to BUN, hemocrit, renal function?

Question of optimal fluid resuscitation still unanswered

- More studies about which patient needs which amout of fluid (severity of disease, comorbidity)