ORIGINAL ARTICLE

# Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis

E. de-Madaria, J.L. Buxbaum, P. Maisonneuve, A. García García de Paredes, P. Zapater, L. Guilabert, A. Vaillo-Rocamora, M.Á. Rodríguez-Gandía, J. Donate-Ortega, E.E. Lozada-Hernández, A.J.R. Collazo Moreno, A. Lira-Aguilar, L.P. Llovet, R. Mehta, R. Tandel, P. Navarro, A.M. Sánchez-Pardo, C. Sánchez-Marin, M. Cobreros, I. Fernández-Cabrera, F. Casals-Seoane, D. Casas Deza, E. Lauret-Braña, E. Martí-Marqués, L.M. Camacho-Montaño, V. Ubieto, M. Ganuza, and F. Bolado, for the ERICA Consortium*

## ABSTRACT

### BACKGROUND

Early aggressive hydration is widely recommended for the management of acute pancreatitis, but evidence for this practice is limited.

### METHODS

At 18 centers, we randomly assigned patients who presented with acute pancreatitis to receive goal-directed aggressive or moderate resuscitation with lactated Ringer's solution. Aggressive fluid resuscitation consisted of a bolus of 20 ml per kilogram of body weight, followed by 3 ml per kilogram per hour. Moderate fluid resuscitation consisted of a bolus of 10 ml per kilogram in patients with hypovolemia or no bolus in patients with normovolemia, followed by 1.5 ml per kilogram per hour in all patients in this group. Patients were assessed at 12, 24, 48, and 72 hours, and fluid resuscitation was adjusted according to the patient's clinical status. The primary outcome was the development of moderately severe or severe pancreatitis during the hospitalization. The main safety outcome was fluid overload. The planned sample size was 744, with a first planned interim analysis after the enrollment of 248 patients.

### RESULTS

A total of 249 patients were included in the interim analysis. The trial was halted owing to between-group differences in the safety outcomes without a significant difference in the incidence of moderately severe or severe pancreatitis (22.1% in the aggressive-resuscitation group and 17.3% in the moderate-resuscitation group; adjusted relative risk, 1.30; 95% confidence interval [CI], 0.78 to 2.18; P=0.32). Fluid overload developed in 20.5% of the patients who received aggressive resuscitation and in 6.3% of those who received moderate resuscitation (adjusted relative risk, 2.85; 95% CI, 1.36 to 5.94, P=0.004). The median duration of hospitalization was 6 days (interquartile range, 4 to 8) in the aggressive-resuscitation group and 5 days (interquartile range, 3 to 7) in the moderate-resuscitation group.

### CONCLUSIONS

In this randomized trial involving patients with acute pancreatitis, early aggressive fluid resuscitation resulted in a higher incidence of fluid overload without improvement in clinical outcomes. (Funded by Instituto de Salud Carlos III and others; WATERFALL ClinicalTrials.gov number, NCT04381169.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. de-Madaria can be contacted at emadaria@umh.es or at Servicio de Aparato Digestivo, Hospital General Universitario Dr. Balmis, Calle Pintor Baeza 12, Alicante 03010, Spain.

*A list of the trial collaborators in the ERICA Consortium is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;387:989-1000.
DOI: 10.1056/NEJMoa2202884

A Quick Take is available at NEJM.org

Moderately severe or severe disease develops in approximately 35% of patients with acute pancreatitis, a situation that is associated with worse outcomes.[1] In animal models, regional hypoperfusion of the pancreas is spatially correlated with necrosis and may be corrected by fluid resuscitation.[2-5] Initial observational studies indicated that hemoconcentration, which is a surrogate for systemic hypovolemia, was associated with pancreatic necrosis.[6,7] Nevertheless, subsequent work indicated that the administration of a greater volume of fluid resuscitation during the first 24 hours may not improve outcomes.[8,9]

Randomized, controlled trials comparing different volumes of intravenous fluid, which were limited by small size and overly specific inclusion criteria, have provided conflicting results.[10] Two trials involving patients with severe pancreatitis showed that rapid fluid expansion was associated with decreased survival.[11,12] A randomized trial[13] involving patients without baseline systemic inflammatory response syndrome (SIRS),[14] who therefore had an initially low risk of moderate-to-severe disease, showed quicker clinical improvement with vigorous hydration than with moderate hydration. A systematic review — although limited by the heterogeneity and quality of the source studies — showed a lower incidence of adverse events and lower mortality with moderate hydration than with aggressive hydration.[15] We initiated WATERFALL (the Early Weight-Based Aggressive vs. Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis: an Open-Label Multicenter Randomized Controlled Trial) 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.

## METHODS

### TRIAL PARTICIPANTS AND OVERSIGHT

In this multicenter, open-label, parallel-group, randomized, controlled, superiority trial, we enrolled patients at 18 centers across four countries (India, Italy, Mexico, and Spain). The complete trial protocol, which has been published previously,[16] is available with the full text of this article at NEJM.org.

Consecutive patients (≥18 years of age) who had received a diagnosis of acute pancreatitis according to the Revised Atlanta Classification (which requires meeting two of the following three criteria: typical abdominal pain, serum amylase or lipase level higher than 3 times the upper limit of the normal range, or signs of acute pancreatitis on imaging) were assessed for eligibility.[17] The trial included patients who presented to the emergency department no more than 24 hours after pain onset and who had received a diagnosis no more than 8 hours before enrollment. Patients who met the criteria for moderately severe or severe disease at baseline (shock, respiratory failure, and renal failure) or who had baseline heart failure (New York Heart Association functional class II, III, or IV), uncontrolled arterial hypertension, hypernatremia, hyponatremia, hyperkalemia, hypercalcemia, an estimated life expectancy of less than 1 year, chronic pancreatitis, chronic renal failure, or decompensated cirrhosis were excluded (see the Supplementary Appendix, available at NEJM.org).

The trial protocol followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines[18] and the principles of the Declaration of Helsinki.[19] All the patients provided written informed consent. An independent data and safety monitoring board comprised a clinical pharmacologist, gastroenterologist, and cardiologist.[16]

The first three authors and the last author designed the trial. The first three authors and the fifth and seventh authors had access to the data and performed the data analysis. The first author vouches for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

### TRIAL PROCEDURES

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).[20] The random-assignment sequence was concealed from the trial team. Randomization was stratified according to trial center, the presence or absence of SIRS, and the presence or absence of baseline hypovolemia.[16]

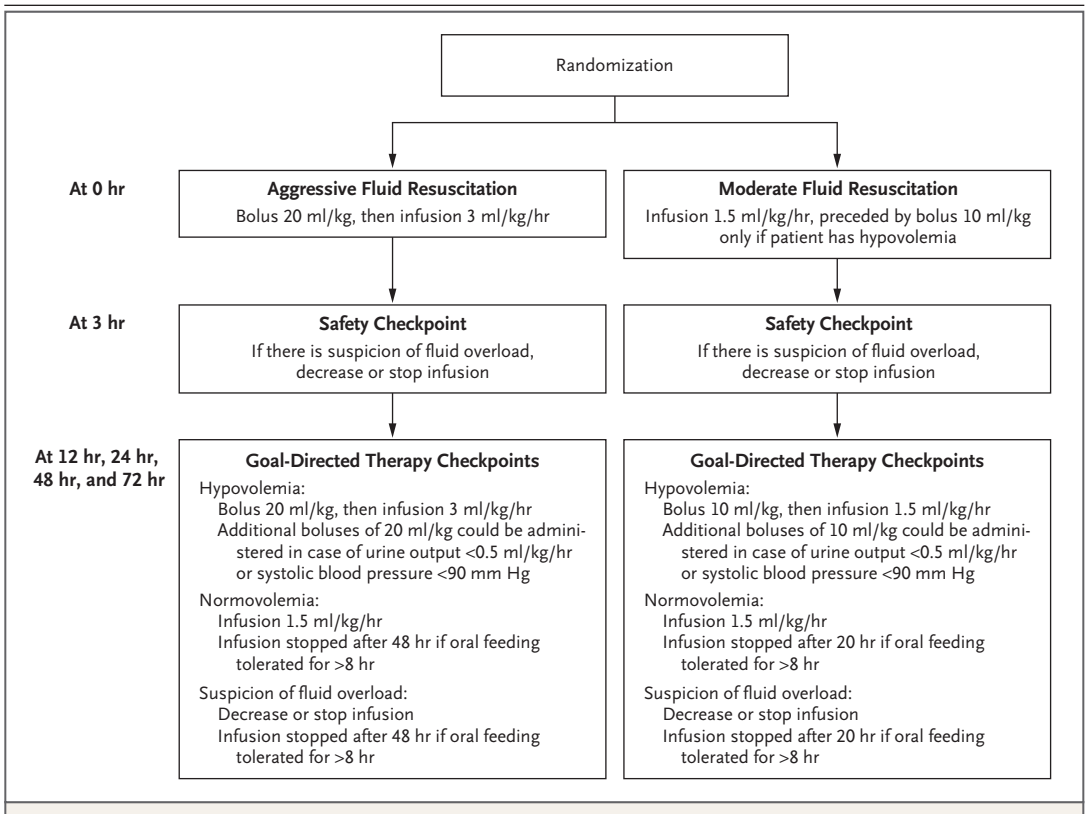


**Figure 1. Fluid Resuscitation Protocol.**

Patients who presented with acute pancreatitis were randomly assigned to receive goal-directed aggressive or moderate fluid resuscitation with lactated Ringer's solution.

The patients and investigators were aware of the assigned trial groups.

In the aggressive-resuscitation group, a bolus of lactated Ringer's solution at a dose of 20 ml per kilogram of body weight was administered over a period of 2 hours, followed by infusion at a rate of 3 ml per kilogram per hour. In the moderate-resuscitation group, patients were given lactated Ringer's solution at a dose of 1.5 ml per kilogram per hour (without a bolus in patients without hypovolemia or after the receipt of a bolus of 10 ml per kilogram administered over a period of 2 hours in patients with hypovolemia). Fluid rates and volumes were based on a previous randomized trial of hydration strategies in acute pancreatitis.[13]

In both trial groups, we performed an initial physical assessment at 3 hours to evaluate for fluid overload and then performed biochemical and physical assessments at 12, 24, 48, and 72 hours. At these checkpoints, goal-directed resuscitation was adjusted (Fig. 1) on the basis of the presence of hypovolemia, normovolemia, or suspicion of fluid overload (see definitions in the Supplementary Appendix). In both groups, hydration was decreased or stopped if there was a suspicion of fluid overload; this strategy was tailored to the degree of fluid overload and to patient-specific characteristics.

Oral feeding was started at 12 hours if the intensity of abdominal pain, as measured on the Patient-Reported Outcome Scale in Acute Pancreatitis (PAN-PROMISE),[21] was less than 5 (range, 0 to 10 for each symptom; overall range, 0 to 70, with higher scores indicating higher symptom intensity). Fluid resuscitation could be stopped once the patient had been able to tolerate oral feeding for 8 hours; in the moderate-resuscitation group, this could occur as early as 20 hours after randomization, and in the aggressive-resuscitation group as early as 48 hours after randomization.

### OUTCOMES

The primary outcome was the development of moderately severe or severe acute pancreatitis (according to the Revised Atlanta Classification) during the hospitalization. Moderately severe or severe acute pancreatitis was defined as the meeting of at least one of the following criteria on the Revised Atlanta Classification: local complications, exacerbation of a preexisting coexisting condition, a creatinine level of at least 1.9 mg per deciliter (170 $\mu$mol 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 ($PaO_2$) to the fraction of inspired oxygen ($FIO_2$) of no more than 300 (see the Supplementary Appendix).[17]

Prespecified secondary outcomes included organ failure and local complications occurring after randomization and during the hospitalization (see the Supplementary Appendix).[16,17] Additional prespecified secondary outcomes included 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; the presence of SIRS (see below) at each checkpoint[14]; 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, persistent organ failure (lasting >48 hours), or infected necrotizing pancreatitis[10]; and symptoms as measured with the use of the PANPROMISE scale at admission and each checkpoint.[21] SIRS was defined as the meeting of at least two of the following criteria: a white-cell count of less than 4000 per cubic millimeter or more than 12,000 per cubic millimeter, a heart rate of more than 90 beats per minute, a respiratory rate of more than 20 breaths per minute or a partial pressure of carbon dioxide of less than 32 mm Hg, or a body temperature of less than 36°C or more than 38°C.[14]

The main safety outcome — fluid overload after randomization and during hospitalization — required the meeting of at least two of the following three criteria: symptoms, physical signs, and imaging evidence of hypervolemia; in addition, the acute respiratory distress syndrome had to be ruled out (see the Supplementary Appendix). To ensure reproducibility, criteria that may have been inconsistently obtained or interpreted at individual trial sites, including auscultation for $S_3$ or $S_4$, orthostatic variables, and effusions on chest radiography (which are frequently exudative in acute pancreatitis) were not used. Fluid overload was graded as mild if it was responsive to medical therapy or decreased hydration and if the ratio of $PaO_2$ to $FIO_2$ never decreased to less than 300; moderate if it was responsive to medical therapy or decreased hydration but the ratio of $PaO_2$ to $FIO_2$ was lower than 300 at least once; and severe if mechanical ventilation or hemofiltration was indicated.

### STATISTICAL ANALYSIS

The anticipated incidence of moderately severe or severe acute pancreatitis was 35%.[1] We calculated that a sample size of 744, with 372 patients in each group, would provide the trial with 80% power to detect a between-group difference of 10 percentage points (between 35% and 25%) at a two-sided significance level (alpha) of 0.05, with an anticipated withdrawal of 10% of the patients. Two interim analyses were planned after one third and two thirds of the patients (248 and 496, respectively) were enrolled; therefore, the sample-size calculation accounted for three sequential tests with the use of the O'Brien–Fleming spending function. There were three a priori stopping rules: a between-group difference in the primary outcome with a two-sided P value of less than 0.0002 at the first interim analysis or of less than 0.012 at the second interim analysis, clear evidence of harm in one trial group over the other (safety) as adjudicated by the data and safety monitoring board, and a slow recruitment rate.[16]

The intention-to-treat population included all the patients who underwent randomization, and the trial data were analyzed according to the intention-to-treat principle. Normality was assessed by the Shapiro–Wilk test. Categorical variables are reported as counts and percentages, and continuous variables as means with standard deviations or medians with interquartile ranges. Differences in continuous variables were compared with the use of a Student's t-test or Mann–Whitney U test. Categorical outcomes were compared with the use of a chi-square test (with Fisher correction when needed) and expressed as a relative risk with a corresponding 95% con-

fidence interval. As a post hoc analysis, the Cochran–Mantel–Haenszel method with adjustment for randomization stratification factors (center, baseline presence or absence of SIRS, and baseline presence or absence of hypovolemia) was used to achieve a more robust analysis,[22] with adjusted relative risks and corresponding 95% confidence intervals.

A two-sided P value of less than 0.05 was considered to indicate statistical significance for the primary efficacy outcome and safety outcomes. Because the statistical analysis plan did not include a provision for correction for multiplicity when tests for secondary or other outcomes were conducted, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Variables with missing values underwent both complete case analysis and analysis after the implementation of the multiple-imputation technique (see the Supplementary Appendix). All the outcomes and statistical analyses were prespecified in the trial protocol,[16] except the multiple imputation for managing variables with missing data and the Cochran–Mantel–Haenszel method to correct for randomization stratification factors. Prespecified subgroup analyses of the efficacy and safety outcomes[16] were performed to determine the influence of baseline hypovolemia and SIRS, because it has been proposed that an early fluid-resuscitation strategy may have greater effect in patients with or without these factors.[13,23] Analyses were performed with the use of SPSS software, version 28.0 (IBM); SAS software, version 9.4 (SAS Institute); and R software, version 4.1.2.

## RESULTS

### PATIENTS

From May 2020 through September 2021, a total of 676 patients with acute pancreatitis were assessed for eligibility. Overall, 249 patients were randomly assigned to the aggressive-resuscitation group (122 patients) or the moderate-resuscitation group (127) and were included in the first interim analysis (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline were evenly distributed between the two trial groups (Table 1). The representativeness of the trial participants with regard to patients with acute pancreatitis is described in Table S1. Sex and cause of disease were representative of patients with acute pancreatitis, but age was younger, which was expected, owing to the exclusion of certain coexisting conditions that are associated with older age (e.g., heart or kidney failure).[1]

Patients in the aggressive-resuscitation group received a median of 7.8 liters (interquartile range, 6.5 to 9.8) of lactated Ringer's solution during the first 48 hours, as compared with 5.5 liters (interquartile range, 4.0 to 6.8) in the moderate-resuscitation group. Details regarding the volume of lactated Ringer's solution administered are provided in Table S3; the greatest between-group difference in volume administration occurred during the first 12 hours.

### EFFICACY OUTCOMES

There was no significant between-group difference in the development of moderately severe or severe acute pancreatitis (primary outcome), which occurred in 22.1% of the patients in the aggressive-resuscitation group and in 17.3% of those in the moderate-resuscitation group (adjusted relative risk, 1.30; 95% confidence interval [CI], 0.78 to 2.18; P=0.32) (Table 2). Organ failure occurred in 7.4% of the patients in the aggressive-resuscitation group and in 3.9% of those in the moderate-resuscitation group (adjusted relative risk, 1.23; 95% CI, 0.47 to 3.23), and local complications occurred in 20.5% and 16.5%, respectively (adjusted relative risk, 1.28; 95% CI, 0.74 to 2.22). Persistent organ failure occurred in 6.6% of the patients in the aggressive-resuscitation group and in 1.6% of those in the moderate-resuscitation group (adjusted relative risk, 2.69; 95% CI, 0.56 to 12.88); respiratory failure in 7.4% and 2.4%, respectively (adjusted relative risk, 2.19; 95% CI, 0.63 to 7.64); and necrotizing pancreatitis in 13.9% and 7.1%, respectively (adjusted relative risk, 1.95; 95% CI, 0.87 to 4.38). A total of 6.6% of the patients in the aggressive-resuscitation group and 1.6% of those in the moderate-resuscitation group were admitted to the ICU (adjusted relative risk, 2.71; 95% CI, 0.64 to 11.51) (Table 2).

The median duration of hospitalization was

**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) |

* Plus–minus values are means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The Charlson comorbidity score ranges from 0 to 37 (plus 1 point for each decade of age starting at 50 years), with higher scores indicating a higher burden of coexisting conditions.[24]
§ The Bedside Index of Severity in Acute Pancreatitis (BISAP) score ranges from 0 to 5, with higher scores indicating higher risk of death.[25] A score of 3 or higher indicates a high probability of adverse outcomes (predicted severe acute pancreatitis).
¶ Overall scores on the Patient-Reported Outcome Scale in Acute Pancreatitis (PAN-PROMISE) range from 0 to 70, with higher scores indicating more severe symptoms of acute pancreatitis.[21] The score at baseline was missing for one patient in the aggressive-resuscitation group.
‖ Patients with systemic inflammatory response syndrome (SIRS) met at least two of the following criteria: a white-cell count of less than 4000 per cubic millimeter or more than 12,000 per cubic millimeter, a heart rate of more than 90 beats per minute, a respiratory rate of more than 20 breaths per minute or a partial pressure of carbon dioxide of less than 32 mm Hg, or a body temperature of less than 36°C or more than 38°C.[14]

6 days (interquartile range, 4 to 8) in the aggressive-resuscitation group and 5 days (interquartile range, 3 to 7) in the moderate-resuscitation group (Table 2). In the complete case analysis, the median PAN-PROMISE score (with higher scores indicating greater symptom intensity) at 12 hours was 23 points (interquartile range, 12 to 35) in the aggressive-resuscitation group and 18 points (interquartile range, 10 to 31) in the moderate-resuscitation group (Table 2). The results of the multiple-imputation method for missing data are provided in Table S2.

### SAFETY OUTCOMES

Aggressive fluid resuscitation was associated with a significantly higher incidence of fluid overload than moderate fluid resuscitation (20.5% vs. 6.3%; adjusted relative risk, 2.85; 95% CI, 1.36 to 5.94) (Table 3). Volume overload was managed as follows: by decreased hydration alone in 12.0% of the patients in the aggressive-resuscitation group and in none of those in the moderate-resuscitation group; by diuretics in 88.0% and 100%, respectively; and by inotropes in 8.0% and none, respectively. One patient in the aggressive-resuscitation group underwent orotracheal intubation, and no patient underwent hemofiltration.

The median time from randomization to fluid overload was 34 hours (interquartile range, 22 to 46) in the aggressive-resuscitation group and 46 hours (interquartile range, 30 to 64) in

the moderate-resuscitation group (P=0.18). Fluid resuscitation was associated with symptoms of fluid overload in 18.0% of the patients in the aggressive-resuscitation group and in 7.9% of those in the moderate-resuscitation group (adjusted relative risk, 1.85; 95% CI, 0.95 to 3.61) and with signs of fluid overload in 26.2% and 11.0%, respectively (adjusted relative risk, 2.36; 95% CI, 1.33 to 4.19). Six patients (4.9%) who received aggressive hydration had moderate-to-severe fluid overload (severe in one patient), as compared with one patient (0.8%) who received moderate hydration, who had moderate fluid overload (adjusted relative risk, 3.62; 95% CI, 0.37 to 35.22). These results were analyzed by the data and safety monitoring board, which halted the trial owing to significantly worse results with respect to safety outcomes in the aggressive-resuscitation group than in the moderate-resuscitation group, which were not balanced by any trend toward improved outcomes.

#### SUBGROUP ANALYSIS

The prespecified subgroup analyses[16] to measure the influence of baseline hypovolemia and baseline SIRS did not yield findings that differed materially from those of the overall analyses (Tables S4 through S9). The prespecified subgroup analysis according to the presence of persistent SIRS (>48 hours) was not performed owing to the scarcity of patients (17) in this subgroup.

## DISCUSSION

This trial showed that aggressive fluid resuscitation increased the risk of volume overload. Given the data showing increased harm without improvement with regard to the primary outcome, the data and safety monitoring board unanimously recommended that the trial be stopped. These findings do not support current management guidelines, which recommend early aggressive resuscitation for the treatment of acute pancreatitis.[26,27] An increased risk of fluid overload was detected in the overall population of patients and also in subgroups of patients without SIRS at baseline, patients with SIRS at baseline (thus, with a higher risk of development of severe pancreatitis), and patients with hypovolemia. Although most episodes of fluid overload with aggressive hydration were nonsevere (the trial was designed to allow early detection and treatment), this situation was not balanced by an improvement in outcomes. In this interim analysis, we found no significant between-group difference in the risk of moderately severe or severe acute pancreatitis (primary outcome). Aggressive fluid resuscitation was associated with a tendency toward a higher intensity of symptoms and a longer duration of hospital stay and a higher incidence of necrotizing pancreatitis than moderate fluid resuscitation. The absence of an efficacy signal for aggressive hydration is of practical importance given that it challenges a strong predilection in many clinicians for the use of early high-volume hydration.[28]

The findings of WATERFALL add to the growing body of evidence that aggressive hydration is linked to worse outcomes in critically ill patients.[29-33] Pancreatitis is associated with increased intraabdominal pressure, which may be worsened by excessive intravenous fluids[30-32]; this adverse effect of aggressive fluid resuscitation may explain the tendency toward a higher intensity of symptoms. The greatest difference in the volume of fluid administered occurred in the first 12 hours, which corresponds to the difference in symptoms at this time point.

Nevertheless, there are several limitations to consider. This trial was terminated at the first interim analysis; thus, it is underpowered to evaluate efficacy outcomes definitively. However, given the small between-group difference in the risk of moderately severe or severe acute pancreatitis, the data and safety monitoring board was concerned that a much larger sample size would be needed for the trial to show superiority in either group, which would expose many patients to a much higher risk of fluid overload.[1,34] The same ethical issues and decision making affected the Fluid Expansion as Supportive Therapy (FEAST) trial, in which intravenous boluses of fluid were associated with unfavorable outcomes in children with severe infection.[35,36]

Another limitation is that this randomized, controlled trial was open-label, which may have introduced bias. Nevertheless, the requirement for trial physicians to evaluate patients sequentially and to adjust the fluid rate to address volume overload or hypovolemia made double-blinding impractical. Even patients in the

**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 |

* The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. The adjusted relative risks with 95% confidence intervals were calculated with the use of Cochran–Mantel–Haenszel estimates with adjustment for variables used for stratified randomization: trial center, baseline presence or absence of SIRS, and baseline presence or absence of hypovolemia. Definitions of outcomes are provided in the Supplementary Appendix. For quantitative variables, the relative risks and adjusted relative risks were calculated for high values (above the median) as compared with low values (at or below the median). ICU denotes intensive care unit, and NA not applicable.

† Presented are complete case analyses in variables with missing data. The analysis after multiple imputation for missing data is shown in Table S2.

‡ P=0.32 for the adjusted relative risk. Categories of the severity of acute pancreatitis were the following: mild, defined as an absence of complications; moderately severe, as transient organ failure or local or systemic complications without persistent organ failure; and severe, as persistent organ failure.

§ Necrotizing pancreatitis was defined as pancreatic or peripancreatic necrosis.

¶ Persistent SIRS was defined as SIRS lasting more than 48 hours.

‖ Nutritional support was defined as the receipt of enteral or parenteral nutrition.

** The relative risk and 95% confidence intervals were calculated by the addition of 0.5 to all values.

†† Persistent organ failure was defined as organ failure lasting more than 48 hours.

‡‡ Most patients in the trial were not admitted to the ICU, so overall, the median number of days in the ICU was 0 (IQR, 0 to 0). In an analysis that included only the 10 patients who were admitted to the ICU, the median ICU stay was 43 days (IQR, 8 to 57) in the aggressive-resuscitation group and 16 days (IQR, 7 to 25) in the moderate-resuscitation group.

**Table 3. Safety Outcomes.***

| Outcome | 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 |

* There were no missing data. Adjusted relative risks and P values were calculated from Cochran–Mantel–Haenszel estimates with adjustment for the variables used for stratified randomization: trial center, baseline presence or absence of SIRS, and baseline presence or absence of hypovolemia. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

† Fluid overload was defined as the meeting of two or more criteria (symptoms or signs of fluid overload or evidence of fluid overload on hemodynamic testing or imaging) and the absence of acute respiratory distress syndrome. A total of 13 patients in the aggressive-resuscitation group and 3 in the moderate-resuscitation group had symptoms and signs; 3 and 0, respectively, had signs and had evidence on hemodynamic testing or imaging; and 9 and 5, respectively, met all three criteria. No patient had only symptoms and evidence on hemodynamic testing or imaging.

‡ The severity of fluid overload was defined as follows: mild, as a response to medical treatment or decrease in volume infusion rate and the ratio of the partial pressure of arterial oxygen ($Pao_2$) to the fraction of inspired oxygen ($Fio_2$) never decreased to less than 300; moderate, as a response to medical treatment or decrease in volume infusion rate and at least one measurement of the ratio of $Pao_2$ to $Fio_2$ of less than 300; and severe, as the use of invasive or noninvasive mechanical ventilation or hemofiltration or death from fluid overload.

§ This relative risk and the 95% confidence interval were calculated by the addition of 0.5 to all values.

moderate-resuscitation group received a liberal volume of fluid, a median of 5.5 liters over a period of 48 hours. It is possible that hydration in the aggressive-resuscitation group may have been too aggressive, and future trials exploring more restrictive strategies should be encouraged.

We mandated a minimum of 48 hours of intravenous fluids in the aggressive-resuscitation group and 20 hours in the moderate-resuscitation group for patients who were tolerating oral intake, which may not reflect real-world practice. Our rationale was that aggressive hydration should continue through the primary period of fluid sequestration.[37] Oral feeding could be started in either trial group at 12 hours if the PAN-PROMISE pain score was less than 5; findings from a recent trial indicate that immediate feeding may be considered in patients with acute pancreatitis,[38] and its effect with regard to fluid resuscitation will also need to be evaluated. Finally, the exclusion of patients at high risk for volume overload could have meant the selection of patients with less severe disease. However, few patients were excluded from the trial owing to acute organ failure.

In our randomized assessment of aggressive fluid resuscitation as compared with moderate fluid resuscitation for the treatment of acute pancreatitis, the use of aggressive fluid resuscitation led to a higher risk of volume overload and did not show the hypothesized benefit in disease-specific outcomes.

Supported by grants from Instituto de Salud Carlos III (PI19/01628, co-funded by the European Commission, European Regional Development Funds), the Spanish Association of Gastroenterology (Gonzalo-Miño 2019), and ISABIAL (Instituto de Investigación Sanitaria y Biomédica de Alicante) (UGP-20-117). Mr. Maisonneuve was supported by the Italian Ministry of Health, Ricerca Corrente, and 5x1000 funds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

The authors' full names and academic degrees are as follows: Enrique de-Madaria, M.D., Ph.D., James L. Buxbaum, M.D., Patrick Maisonneuve, Dipl.Eng., Ana García García de Paredes, M.D., Ph.D., Pedro Zapater, M.D., Ph.D., Lucía Guilabert, M.D., Alicia Vaillo-Rocamora, Pharm.D., Miguel Á. Rodríguez-Gandía, M.D., Jesús Donate-Ortega, M.D., Edgard E. Lozada-Hernández, M.D., Alan J.R. Collazo Moreno, M.D., Alba Lira-Aguilar, M.D., Laura P. Llovet, M.D., Rajiv Mehta, M.D., Raj Tandel, M.D., Pablo Navarro, M.D., Ana M. Sánchez-Pardo, M.D., Claudia Sánchez-Marin, M.D., Marina Cobreros, M.D., Idaira Fernández-Cabrera, M.D., Fernando Casals-Seoane, M.D., Ph.D., Diego Casas Deza, M.D., Eugenia Lauret-Braña, M.D., Ph.D., Eva Martí-Marqués, M.D., Laura M. Camacho-Montaño, M.D., Verónica Ubieto, M.D., Mikel Ganuza, M.D., and Federico Bolado, M.D., Ph.D.

The authors' affiliations are as follows: the Departments of Gastroenterology (E.M., L.G., A.V.-R.) and Clinical Pharmacology (P.Z.), Dr. Balmis General University Hospital, ISABIAL (Instituto de Investigación Sanitaria y Biomédica de Alicante), Alicante, the Department of Clinical Medicine, Faculty of Medicine, Miguel Hernández University, Elche (E.M.), the Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Universidad de Alcalá (A.G.G.P., M.Á.R.-G., J.D.-O.), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (P.Z., F.C.-S.), and the Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (F.C.-S.), Madrid, the Gastroenterology and Digestive Endoscopy Unit, Corporació Sanitària Parc Taulí, Sabadell (A.L.-A., L.P.L.), the Department of Gastroenterology, Hospital Clínico Universitario de Valencia, Valencia (P.N., A.M.S.-P.), the Department of Gastroenterology and Hepatology, Marqués de Valdecilla University Hospital, Santander (C.S.-M., M.C.), the Department of Gastroenterology, Hospital Dr. Negrín, Las Palmas (I.F.-C.), the Department of Gastroenterology, Miguel Servet University Hospital and Health Research Institute of Aragón, Zaragoza (D.C.D.), the Department of Gastroenterology, Central de Asturias University Hospital, Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo (E.L.-B.), the Department of Gastroenterology, Lucus Augusti University Hospital, Lugo (E.M.-M.), the Department of Gastroenterology, Puerta del Mar University Hospital, Cadiz (L.M.C.-M.), and the Department of Gastroenterology, University Hospital of Navarre, Pamplona (V.U., M.G., F.B.) — all in Spain; the Division of Gastroenterology, University of Southern California, Los Angeles (J.L.B.); the Division of Epidemiology and Biostatistics, IRCSS European Institute of Oncology, Milan (P.M.); the General Surgery Unit, Department of Diseases of the Digestive Tract, Regional Hospital of High Specialty of Bajío, Leon, Mexico (E.E.L.-H., A.J.R.C.M.); and the Department of Gastroenterology, Surat Institute of Digestive Sciences Hospital and Research Center, Surat, India (R.M., R.T.).

## REFERENCES

1. Sternby H, Bolado F, Canaval-Zuleta HJ, et al. Determinants of severity in acute pancreatitis: a nation-wide multicenter prospective cohort study. Ann Surg 2019; 270:348-55.
2. Kinnala PJ, Kuttila KT, Grönroos JM, Havia TV, Nevalainen TJ, Niinikoski JH. Splanchnic and pancreatic tissue perfusion in experimental acute pancreatitis. Scand J Gastroenterol 2002;37:845-9.
3. Kusterer K, Enghofer M, Zendler S, Blöchle C, Usadel KH. Microcirculatory changes in sodium taurocholate-induced pancreatitis in rats. Am J Physiol 1991; 260:G346-G351.
4. Juvonen PO, Tenhunen JJ, Heino AA, et al. Splanchnic tissue perfusion in acute experimental pancreatitis. Scand J Gastroenterol 1999;34:308-14.
5. Niederau C, Crass RA, Silver G, Ferrell LD, Grendell JH. Therapeutic regimens in acute experimental hemorrhagic pancreatitis: effects of hydration, oxygenation, peritoneal lavage, and a potent protease inhibitor. Gastroenterology 1988;95:1648-57.
6. Baillargeon JD, Orav J, Ramagopal V, Tenner SM, Banks PA. Hemoconcentration as an early risk factor for necrotizing pancreatitis. Am J Gastroenterol 1998;93: 2130-4.
7. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. Pancreas 2000;20:367-72.
8. Singh VK, Gardner TB, Papachristou GI, et al. An international multicenter study of early intravenous fluid administration and outcome in acute pancreatitis. United European Gastroenterol J 2017;5: 491-8.
9. de-Madaria E, Soler-Sala G, Sánchez-Payá J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. Am J Gastroenterol 2011;106:1843-50.
10. Vege SS, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute technical review. Gastroenterology 2018; 154:1103-39.
11. Mao EQ, Tang Y-Q, Fei J, et al. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl) 2009;122:169-73.
12. Mao E-Q, Fei J, Peng Y-B, Huang J, Tang Y-Q, Zhang S-D. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Chin Med J (Engl) 2010;123:1639-44.
13. Buxbaum JL, Quezada M, Da B, et al. Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. Am J Gastroenterol 2017;112:797-803.
14. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74.
15. Di Martino M, Van Laarhoven S, Ielpo B, et al. Systematic review and meta-analysis of fluid therapy protocols in acute pancreatitis: type, rate and route. HPB (Oxford) 2021;23:1629-38.
16. Bolado F, Buxbaum JL, Vaillo-Rocamora A, Cárdenas-Jaén K, Maisonneuve P, de-Madaria E. Early weight-based aggressive vs. non-aggressive goal-directed fluid resuscitation in the early phase of acute pancreatitis: an open-label multicenter randomized controlled trial (the WATERFALL trial), design, and rationale. Front Med (Lausanne) 2020;7:440.
17. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis — 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
18. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.
19. World Medical Association. World

Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
**20.** Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.
**21.** de-Madaria E, Sánchez-Marin C, Carrillo I, et al. Design and validation of a patient-reported outcome measure scale in acute pancreatitis: the PAN-PROMISE study. Gut 2021;70:139-47.
**22.** Kahan BC, Morris TP. Adjusting for multiple prognostic factors in the analysis of randomised trials. BMC Med Res Methodol 2013;13:99.
**23.** Wu BU, Bakker OJ, Papachristou GI, et al. Blood urea nitrogen in the early assessment of acute pancreatitis: an international validation study. Arch Intern Med 2011;171:669-76.
**24.** Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
**25.** Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut 2008;57:1698-703.
**26.** Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-16.
**27.** Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:Suppl 2:e1-e15.
**28.** Gardner TB. Acute pancreatitis. Ann Intern Med 2021;174(2):ITC17-ITC32.
**29.** Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
**30.** Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015;19:251.
**31.** Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42:1695-705.
**32.** Messmer AS, Zingg C, Müller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid overload and mortality in adult critical care patients — a systematic review and meta-analysis of observational studies. Crit Care Med 2020;48:1862-70.
**33.** Malbrain ML, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther 2014;46:361-80.
**34.** Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut 2004;53:1340-4.
**35.** Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483-95.
**36.** Todd J, Heyderman RS, Musoke P, Peto T. When enough is enough: how the decision was made to stop the FEAST trial: data and safety monitoring in an African trial of fluid expansion as supportive therapy (FEAST) for critically ill children. Trials 2013;14:85.
**37.** de-Madaria E, Banks PA, Moya-Hoyo N, et al. Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis. Clin Gastroenterol Hepatol 2014;12:997-1002.
**38.** Ramírez-Maldonado E, López Gordo S, Pueyo EM, et al. Immediate oral refeeding in patients with mild and moderate acute pancreatitis: a multicenter, randomized controlled trial (PADI trial). Ann Surg 2021;274:255-63.