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Conservative Fluid Management after Sepsis Resuscitation: A Pilot Randomized Trial

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Abstract

RATIONALE: The feasibility and clinical outcomes of conservative fluid management after sepsis resuscitation remain unknown.

OBJECTIVES: To evaluate the effect of a conservative fluid management protocol on fluid balance and intensive care unit (ICU)-free days among patients with sepsis.

METHODS: In a single-center phase II/III randomized trial, we enrolled adults with suspected infection, ≥ 2 systemic inflammatory response syndrome criteria, and either shock (mean arterial pressure < 60 mmHg or vasopressors) or respiratory insufficiency (mechanical ventilation or oxygen saturation < 97% and fraction of inspired oxygen ≥ 0.3). Patients were randomized 1:1 to usual care or a conservative fluid management protocol. The protocol restricted intravenous fluid administration during shock to treatment of oliguria or increasing vasopressor requirement. In the absence of shock, loop diuretic infusion targeted equal fluid input and output each study day. The primary outcomes were mean daily fluid balance (Phase II) and ICU-free days (Phase III).

RESULTS: At the completion of Phase II (n=30), the difference in mean daily fluid balance between groups (−398 mL) was less than the pre-specified threshold (−500 mL) and the trial was stopped. Patients in the conservative fluid management (n=15) and usual care (n=15) groups experienced similar cumulative fluid input (8,450 vs 7,049 mL; $P = .90$), of which only 14% was

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Authors contributions: Study concept and design: M.W.S, D.R.J., and T.W.R.; Acquisition of data: M.W.S., J.D.C., and T.W.R.; Analysis and interpretation of data: M.W.S, D.R.J., J.D.C., W.H.S., and T.W.R.; Drafting of the manuscript: M.W.S.; Critical revision of the manuscript for important intellectual content: M.W.S, D.R.J., J.D.C., W.H.S., and T.W.R.; Statistical analysis: M.W.S.; Study supervision: M.W.S. and T.W.R.. M.W.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.W.S. conducted and is responsible for the data analysis.

Subject Descriptor Number: 4.4 Clinical Trials in Critical Care Medicine

CONFLICTS OF INTEREST

All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors declared no potential conflicts of interest with the current work. W.H.S. reported serving on advisory boards for Venaxis, Inc., Ferring Pharmaceuticals, and Cempra Pharmaceuticals, and as a consultant for Abbott Point-of-Care. T.W.R. reported serving on an advisory board for Avisa Pharma, LLC and as the Director of Medical Affairs for Cumberland Pharmaceuticals, Inc.

intravenous crystalloid or colloid. Loop diuretic infusion occurred more frequently in the conservative fluid management group (40% vs 0%; $P = 0.02$) and cumulative fluid output was 10,645 mL in the conservative fluid management group compared with 6,286 mL in the usual care group ($P = .39$). Hemodynamic, respiratory, and renal function did not differ between groups.

CONCLUSIONS: In this Phase II trial, a conservative fluid management protocol did not decrease mean daily fluid balance by more than 500 mL among patients with sepsis.

REGISTRATION: Clinicaltrials.gov; NCT02159079

Keywords

Sepsis; intravenous fluid; acute kidney injury

INTRODUCTION

Early intravenous fluid administration is a fundamental therapy for sepsis[1,2] and has been the subject of significant recent research[3–7]. In contrast, few data are available to inform the optimal approach to fluid management after initial sepsis resuscitation[8,9]. Guidelines have recommended fluid administration be continued as long as hemodynamic improvements persist[10] and observational studies report net fluid balances of 5–11 liters positive during the first week of sepsis management[11–15]. After resuscitation, however, the potential benefits of fluid administration are weighed against the risks of organ edema and detrimental effects of the fluid constituents[16–18]. Numerous observational studies have associated positive fluid balance in sepsis with organ dysfunction and mortality[11,15,19]. However, only two pilot trials have prospectively examined post-resuscitation fluid management in sepsis[8,9]. Whether a conservative fluid management strategy after sepsis resuscitation results in a clinically meaningful difference in fluid balance or impacts outcomes compared to usual care remains unknown[20].

We designed a phase II/III randomized trial to assess the feasibility (Phase II) and clinical effects (Phase III) of a protocol targeting neutral fluid balance after sepsis resuscitation. We hypothesized that this conservative fluid management protocol would decrease mean daily fluid balance (Phase II) and increase days alive and free of the intensive care unit (ICU) (Phase III) compared with usual care.

METHODS

Study Design and Oversight

The BALANCE (“Phase II/III Randomized Controlled Trial of a Conservative Fluid Balance Strategy for Patients with Sepsis and Cardiopulmonary Dysfunction”) study was a single-center, un-blinded, parallel-group, randomized trial comparing a conservative fluid management protocol to usual care among adults with sepsis and shock or respiratory insufficiency. Phase II compared conservative fluid management to usual care with regard to mean daily fluid balance among 30 patients. If the conservative fluid management protocol produced a mean daily fluid balance at least 500 mL less than usual care in Phase II, Phase III planned to enroll an additional 120 patients to compare ICU-free days between groups.

The study protocol (available in the online supplement) was approved by the institutional review board at Vanderbilt University (IRB#140582) and the trial was registered online prior to initiation (NCT02159079).

Patient Population

From August 23, 2014 to February 25, 2016 we recruited adults (age ≥ 18 years) admitted to the medical ICU at Vanderbilt University Medical Center who met two or more criteria for systemic inflammatory response syndrome[21], were receiving antimicrobial therapy, and met criteria either for shock (defined as a mean arterial pressure < 60 mmHg or vasopressor receipt) or respiratory insufficiency (defined as receipt of invasive or non-invasive mechanical ventilation or an arterial oxygen saturation < 97% while receiving a fraction of inspired oxygen (FiO_2) ≥ 0.3). Exclusion criteria are described in the online supplement. All patients or their legally authorized representatives provided written informed consent prior to enrollment.

Randomization

Patients were randomized in a 1:1 ratio to conservative fluid management or usual care using computer-generated blocks of 2, 4 and 6, stratified by the presence or absence of shock. Group assignment remained concealed until a patient had qualified for enrollment, consent had been provided, and at least 12 hours had elapsed since ICU admission.

Study Interventions

In both groups, the study began at randomization (which occurred at the later of informed consent or 12 hours after ICU admission) and ended at study termination (which occurred at the first of ICU discharge, 14 days after enrollment, cessation of vasopressors and return of the patient's FiO_2 to pre-admission baseline, or death).

For patients assigned to usual care, all aspects of patient care including fluid management were deferred to treating clinicians. For patients assigned to the conservative fluid management group, fluid and diuretic therapy were governed by a fluid management protocol (available in the online supplement). This protocol was modeled on the simplified conservative fluid management protocol developed by the National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network targeting equal fluid intake and output in the 7 days after enrollment[22,23] and refined by a multidisciplinary expert panel (see online supplement).

Upon initiation of the protocol, intravenous fluids being administered to maintain intravascular volume or replace insensible losses ("maintenance fluids") were discontinued and the pharmacy maximally concentrated all intravenous medications. For patients in shock (mean arterial pressure < 60 mmHg or vasopressor receipt in the prior 12 hours), intravenous fluid boluses were administered only for oliguria (urine output < 30 mL/h for 6 hours) or increasing vasopressor requirement. For patients without shock, intravenous fluid boluses were permitted only for oliguria, and continuous furosemide infusion beginning at 3 mg/h and titrated as high as 24 mg/h was administered, as needed, to achieve a total fluid output greater than total fluid input for each 24 hour study day. The protocol was suspended only

for the initiation of renal replacement therapy (RRT), receipt of at least 60 mcg/min of norepinephrine or increase in norepinephrine of greater than 20 mcg/min over 6 hours, or acute clinical decompensation (see online supplement). Patients, treating clinicians, and investigators were not blinded to study group assignment.

Data Collection

Data were collected at enrollment, daily for 14 days, and at study termination. Collected data included: baseline demographics, comorbidities, pre-enrollment sepsis management, measures of hemodynamic, respiratory, and renal function, severity of illness; hourly assessments of blood pressure, vasopressor receipt, and urine output; daily assessments of fluid input, fluid output, and diuretic receipt; daily assessments of hemodynamic and respiratory function, plasma laboratory values, and receipt of mechanical ventilation, vasopressors, and RRT; and blinded assessment of vital status, timing of liberation from mechanical ventilation, ICU transfer, and hospital discharge at 28 days after enrollment. Each patient's chest radiographs were independently reviewed by two pulmonologists blinded to study group assignment for radiographic evidence of acute respiratory distress syndrome (ARDS) by Berlin criteria[24].

Study Outcomes

The primary outcomes were mean daily fluid balance for Phase II and days alive and free of ICU admission in the 14 days after enrollment (ICU-free days) for Phase III. Daily fluid balance was calculated as total fluid input minus total fluid output between enrollment and study termination, divided by the number of days between enrollment and study termination. Secondary outcomes included in-hospital mortality, vasopressor-free days, ventilator-free days, renal-failure free days, highest stage of acute kidney injury by Kidney Disease Improving Global Outcomes (KDIGO) criteria[25], highest plasma creatinine, change from baseline to highest plasma creatinine, and change from enrollment to highest plasma creatinine.

Statistical Analysis

For Phase II, a minimum difference between groups in mean daily fluid balance of 500 mL was selected as the threshold to continue to Phase III. This 500 ml threshold was based on a prior trial of conservative fluid management in ARDS in which a 1,000 mL difference in daily fluid balance between groups resulted in an absolute increase in ICU-free days of 2 days[26]. When designing the current trial, we felt that a difference between groups in mean daily fluid balance less than 500 mL was unlikely to produce a significant difference in clinical outcomes.

For Phase III, we calculated that enrollment of 150 patients would provide 80% power at an alpha level of 0.05 to detect a 2.0 day absolute increase in ICU-free days in the conservative fluid group compared to the usual care group, assuming the mean for ICU free days in the usual care group was 6.8 days and the standard deviation was 4.3 days. These assumptions were based on a prior sepsis cohort study in the same ICU[27].

All analyses were conducted in an intention-to-treat fashion. Continuous variables were reported as mean ± standard deviation or median and interquartile range; categorical variables as frequencies and proportions. Between-group comparisons were made with the Mann-Whitney rank sum test for continuous variables, Fisher's exact test or chi-square test for categorical variables, and multivariable regression for adjusted analyses and tests of interaction. A two-sided P value < 0.05 determined significance. Analyses were performed using SPSS Statistics v.24 (IBM Corp., Armonk, NY, USA) or R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Enrollment and Baseline Characteristics

Of 192 patients screened, 30 patients (15.6%) were eligible, provided informed consent, and were enrolled; an average rate of enrollment of 1.6 patients per month. After enrollment of 30 patients in the Phase II portion of the trial, the difference in mean daily fluid balance between groups was −398 mL (95% CI −1,227 to 430 mL; $P = .33$). This difference in mean daily fluid balance did not meet the pre-specified 500 ml threshold for continuing to Phase III and the trial was stopped (Figure 1).

Patients randomized to conservative fluid management (n=15) and usual care (n=15) were similar at baseline (Table 1). All patients received antibiotics before enrollment (Table E1). The median time from ICU admission to enrollment was 13.8 hours, median time from enrollment to randomization was 3.5 minutes, and median time from randomization to protocol initiation in the conservative fluid management group was 2.0 minutes (Table E1).

Fluid Balance

The difference between groups in mean daily fluid balance, the primary outcome for Phase II, was −398 mL (95% CI −1,227 to 430 mL; $P = .33$) (Figure 2–3). Cumulative fluid balance (total fluid input minus total fluid output) over the course of the study was −2,195 ± 4,313 mL in the conservative fluid management group compared with 764 ± 4,352 mL in the usual care group (mean difference −2,959 mL; 95% CI −6,199 to 282 mL; $P = .11$) (Figure 2). A total of 10 patients (66.7%) in the conservative fluid management group and 6 patients (40.0%) in the usual care group had a net negative fluid balance at 14 days ($P = .14$).

Fluid Administration

In the 3 days after enrollment, a total of 14 IV fluid boluses were administered among the 15 patients in usual care group, compared with 5 IV fluid boluses among the 15 patients in the conservative group (Table E2). The only patient to receive a fluid bolus more than 3 days after enrollment was a patient in the conservative arm who received three 500 mL IV fluid boluses on study day 8 for oliguria. All fluid boluses administered in the conservative fluid management group were compliant with study protocol and administered for either oliguria (n=6) or increase in vasopressor requirement (n=2). Of the 14 fluid boluses given to patients in the usual care arm, 2 were for oliguria, 3 were for increasing vasopressor requirement, and 9 were administered in the absence of oliguria or increasing vasopressor requirement. Over the course of the trial, patients in the usual care group received a mean volume of fluid

from IV boluses of 733 ± 1,083 compared with 300 ± 560 in the conservative fluid management group ($P = .30$).

Between enrollment and study day 14, the pharmacy concentrated medication infusions for 15 (100%) patients in the conservative fluid management group based on study protocol and 1 patient (6.7%) in the usual care group based on clinician request ($P < .001$).

Cumulative fluid input between enrollment and study termination was similar between the conservative fluid management group (8,450 ± 10,103 mL) and usual care group (7,049 ± 6,459) ($P = .90$) (Figure 2). Most fluid input derived from IV mediations (37%), enteral nutrition (30%), and enteral free water (17%) rather than administration of IV crystalloids (14%), colloids (0%), or blood products (2%) (Table E3).

Diuretic Administration and Fluid Output

The mean cumulative furosemide dose received in the conservative fluid management group was 133 ± 361 mg versus 33 ± 68 mg in the usual care group ($P = 0.34$) (Table E2). Receipt of loop diuretic as a continuous infusion was more common for patients in the conservative fluid management group than in the usual care group (40% vs 0%; $P = 0.02$).

The 15 patients in the conservative fluid management group contributed a total of 56 patient-days alive and in the intensive care unit, on 23 (41.1%) of which vasopressors were administered such that study protocol did not dictated diuretic infusion. Of the remaining 33 patient-days, on 15 patient-days (45.5%) a diuretic infusion was administered (compliant with protocol), on 12 patient-days (36.4%) a diuretic infusion was not administered because the patient was net negative without diuretic infusion (compliant with protocol), and on 5 patient-days (15.2%) a diuretic infusion was not administered and the patient was net positive (non-compliant with protocol). The total volume net positive on each of these five non-compliant patient-days was 40 mL, 225 mL, 306 mL, 388 mL, and 934 mL, respectively. For patient-days on which a diuretic infusion was administered, the mean daily dose of loop diuretic in furosemide equivalents was 130 ± 116 mg/day, and the mean maximum hourly infusion rate was 10 ± 9 mg/hour.

Cumulative fluid output over the course of the study was 10,645 ± 11,733 mL in the conservative fluid management group compared with 6,286 ± 5,870 mL in the usual care group ($P = .39$) (Figure 2).

Hemodynamic, Laboratory, Radiographic, and Clinical Outcomes

Conservative fluid management did not overtly affect patients' hemodynamics, respiratory function, duration of mechanical ventilation or vasopressor receipt, development of acute kidney injury, or receipt of renal replacement therapy (Table 2, Table E4–7). Only two patients (13.3%) in each study group experienced a plasma sodium concentration greater than 145 mmol/L in the first 14 days ($P > .99$). The conservative fluid management and usual care groups did not differ significantly with regard to in-hospital mortality (30.0% vs 26.7%, respectively; $P > .99$) or number of ICU-free days to day 14 (11 vs 9, respectively; $P > .99$) (Table 2).

DISCUSSION

In this pilot trial, a conservative fluid management protocol did not decrease mean daily fluid balance by the pre-specified threshold (500 mL per day) among patients with post-resuscitation sepsis. Despite achieving fluid output greater than input on every study day in the conservative fluid management arm, lower than anticipated IV fluid administration in usual care impeded separation between groups. These findings have important implications for the design and conduct of future studies of fluid management in sepsis.

Although numerous studies have evaluated fluid administration during sepsis resuscitation[3–6,28,29], only three trials inform fluid management after resuscitation: the Fluid and Catheter Treatment Trial (FACTT)[26] and two recent pilot studies of fluid restriction after sepsis resuscitation[8,9]. FACTT compared liberal versus conservative fluid management among 1,000 ventilated ARDS patients, 70% of whom had underlying infection[26]. In the liberal arm, cumulative fluid input exceeded output by 7 liters at 7 days compared to equal input and output in the conservative arm, resulting in a difference of 2 ventilator-free days and 2 ICU-free days between groups. In contrast, both recent pilot trials targeting fluid restriction after sepsis resuscitation achieved a numerical difference between groups in cumulative fluid balance by 5 days of around 1 liter[8,9], with no differences in clinical outcomes.

Why did our trial fail to achieve the pre-specified separation in fluid balance between groups? One explanation is that fluid management in usual care was significantly different than anticipated. Unlike prior observational studies that reported fluid balances of five or more liters positive in the week after sepsis resuscitation[11,19], patients in the usual care arm of our trial averaged less than 1 liter net positive in the 7 days after enrollment. Several factors may explain this unexpectedly low fluid balance. Inclusion of patients without shock may have selected sepsis patients who received less IV fluid. Beginning the trial 12 hours after ICU admission may have missed the period of greatest fluid administration. Current usual care may have shifted toward less fluid administration compared to historical cohorts.

Alternatively, our pre-specified threshold for separation in fluid balance between groups may have been unnecessarily large. When designing the trial, we felt that the difference in fluid balance would need to be at least 500 mL a day (half the daily difference in FACTT[26]) to exert a meaningful effect on organ edema and clinical outcomes. Recent data, however, suggest that even relatively small volumes of IV fluid may impact clinical outcomes[6,7,29,30]. When designing future trials of conservative fluid management in sepsis, consideration should be given to targeting more modest differences in absolute measures of fluid balance between groups.

In addition to the above, our study is limited by conduct at a single center, small sample size, and lack of blinding. The conservative fluid management protocol was developed by consensus – and may be subject to critique. Some experts would advocate for inclusion of dynamic measures of “fluid responsiveness” [31], but there are not yet data that guiding fluid administration by “fluid responsiveness” improves clinical outcomes. Our study attempted to control fluid management for 14 days, which was longer than prior trials and may be too

long a time-period over which to effectively achieve separation between groups. Although we coordinated with the pharmacy to concentrate amenable medications, this did not result in a difference in medication volumes between groups. Additionally, targeting a 2.0 day absolute increase in ICU-free days in the phase III portion of the trial may have been overly ambitious for an intervention designed to decrease fluid balance by only 500 mL per day.

Our study also has several strengths. Despite most patients receiving vasopressors at enrollment, the conservative fluid management protocol achieved an average “net negative” fluid balance on each study day (without any overt harmful effects on clinical outcomes). The numerical difference between groups in cumulative fluid balance was greater than in any prior sepsis fluid management trial[3–5,8,9,28]. Strong compliance with fluid and diuretic administration instructions based on hourly blood pressure and urine output measurements demonstrates that adherence to an intensive study protocol is feasible.

Based on our findings, future trials of conservative fluid management in sepsis should: target patients likely to receive ongoing fluid administration; control fluid and diuretics in both study arms to prevent drift in usual care; and consider enrollment prior to ICU admission to control the period of highest fluid exposure.

CONCLUSIONS

In this pilot trial, a conservative fluid management protocol did not decrease mean daily fluid balance by ≥ 500 mL among patients with post-resuscitation sepsis. These findings may inform the design of future trials examining fluid management in sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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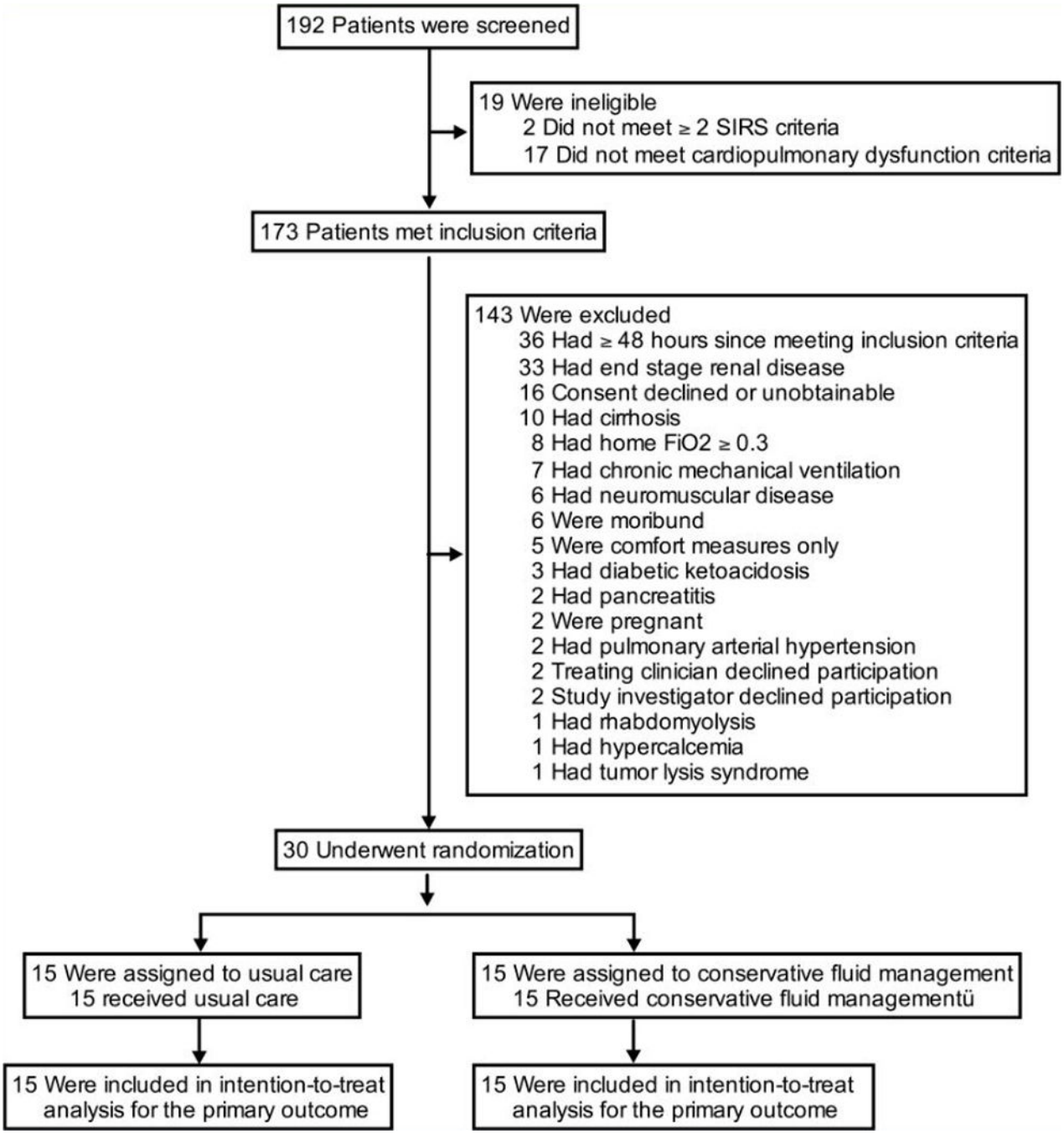

Figure 1. Flow of participants through the trial.

Of 192 patients screened, 30 met inclusion criteria without meeting exclusion criteria and were enrolled, randomized, followed, and analyzed. Two potentially eligible patients were excluded by study investigators, one receiving scheduled fluid boluses prior to amphotericin administration and one with septic shock in the context of severe mitral stenosis. SIRS = systemic inflammatory response syndrome, cardiopulmonary dysfunction criteria = shock (mean arterial pressure < 60 mmHg or vasopressor receipt) or respiratory insufficiency

(mechanical ventilation or oxygen saturation < 97% with fraction of inspired oxygen ≥ 0.3), FiO2 = fraction of inspired oxygen

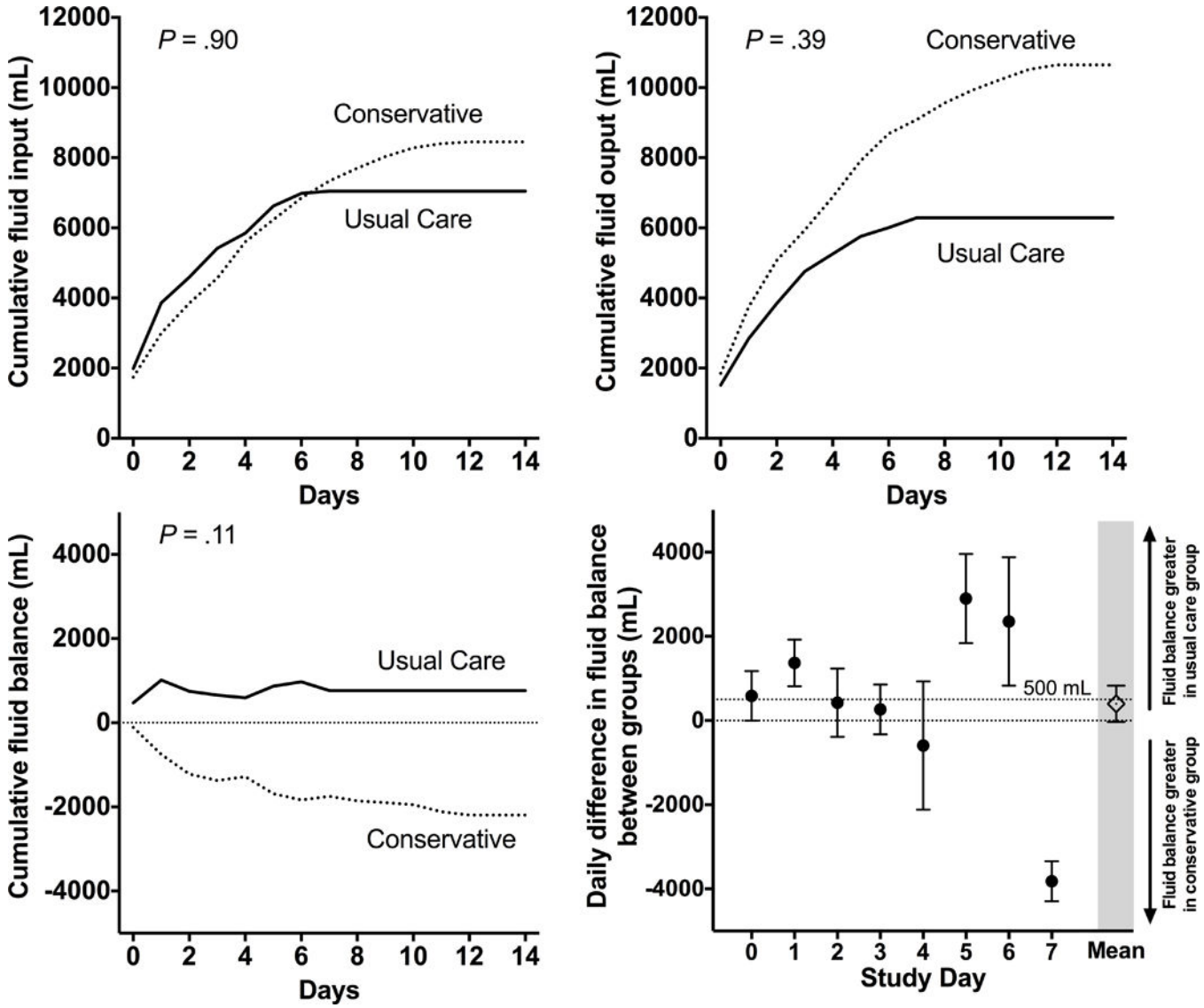

Figure 2. Fluid management by study group.

Cumulative fluid input (upper left panel), fluid output (upper right panel), and fluid balance (lower left panel) among patients in the conservative fluid management group (dotted line) and usual care group (solid line). The lower right panel displays the mean difference between groups in fluid balance on each study day. The diamond (mean) and bars (standard deviation) display the primary outcome of the difference between groups in mean daily fluid balance over the course of the trial. The numbers of patients in the conservative fluid management and usual care groups, respectively, were: 15 and 15 (day of enrollment), 14 and 14 (day 1), 10 and 9 (day 2), 7 and 8 (day 3), 5 and 3 (day 4), 4 and 3 (day 5), 2 and 1 (day 6), and 2 and 1 (day 7). The increase in cumulative fluid input in the conservative fluid management group on study days 7 and 8 resulted from a single patient who received 5,850 mL of oral free water over 48 hours for a sodium of 150 mmol/L.

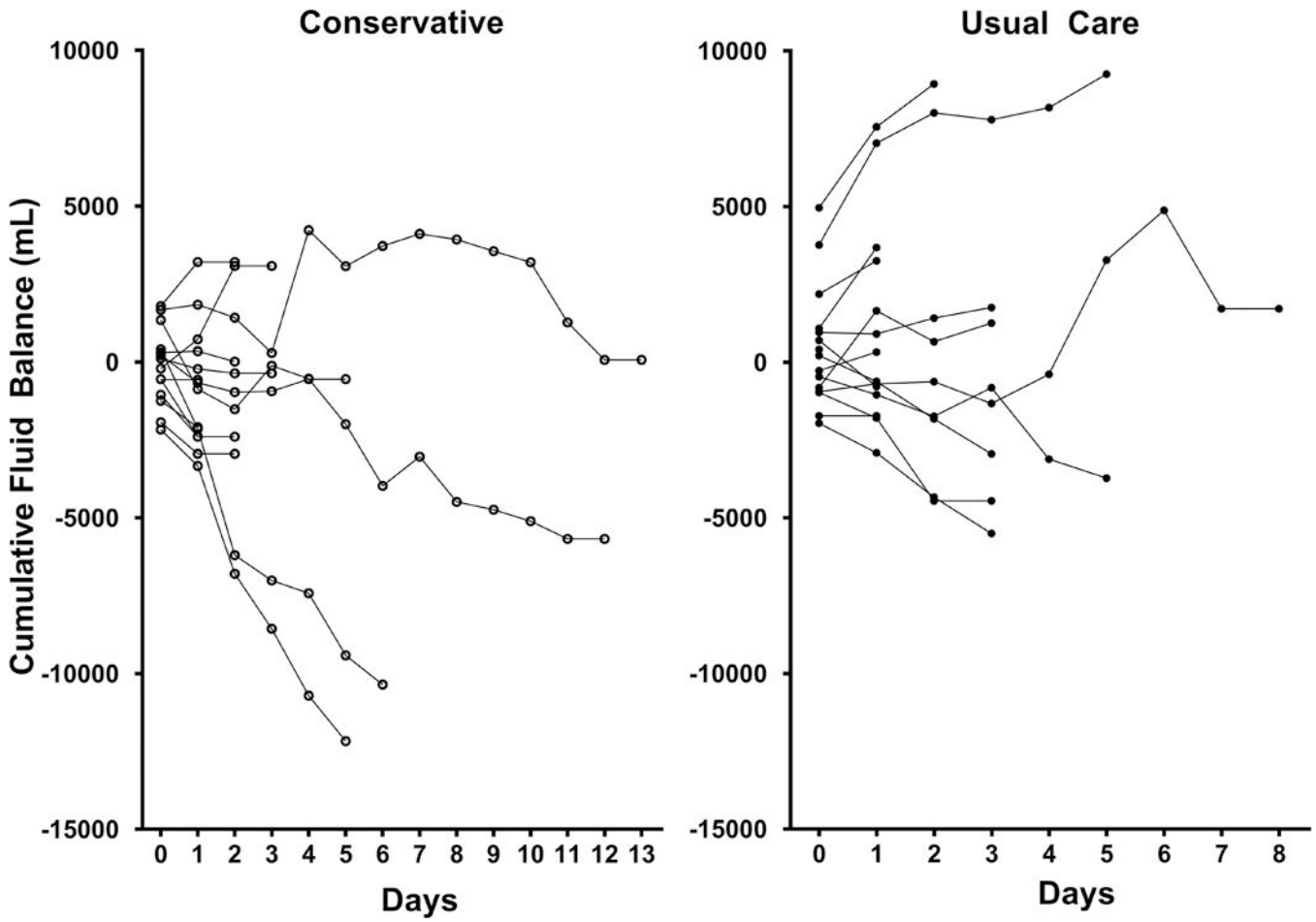

Figure 3. Cumulative Fluid Balance for Each Individual Patient.

For patients in the conservative fluid management group (left) and usual care group (right), the cumulative fluid balance is displayed for each study day. Data are censored at the time of death or transfer out of the intensive care unit.

Table 1.

Patient characteristics at baseline.

Patient Characteristics	Usual Care (n = 15)	Conservative (n = 15)
Age, median [IQR], years	65 [57 – 77]	61 [54 – 75]
Men, No. (%)	8 (53.3)	7 (46.7)
Caucasian, No. (%)	14 (93.3)	14 (93.3)
Body mass index, median [IQR], kg/m^2	27.8 [26.0 – 32.7]	28.9 [22.2 – 37.0]
Comorbidities, No. (%)		
Congestive heart failure	1 (6.7)	3 (21.4)
Chronic kidney disease, stage III or greater *	3 (20.0)	1 (6.7)
Immunosuppression	7 (46.7)	5 (33.3)
Suspected site of infection, No. (%)		
Pulmonary	9 (60.0)	8 (53.3)
Urinary	1 (6.7)	2 (13.3)
Bacteremia	2 (13.3)	1 (6.7)
Intra-abdominal	0 (0.0	2 (13.3)
Central nervous system	0 (0.0)	2 (13.3)
Bone and joint	1 (6.7)	0 (0.0)
Unknown	2 (13.3)	0 (0.0)
Source of admission to ICU, No. (%)		
Emergency department	7 (46.7)	6 (40.0)
Transfer from another hospital	5 (33.3)	8 (53.3)
Hospital ward	3 (20.0)	0 (0.0)
Another ICU within the hospital	0 (0.0)	1 (6.7)
Invasive mechanical ventilation, No. (%)	4 (26.7)	7 (46.7)
Noninvasive mechanical ventilation, No. (%)	2 (13.3)	1 (6.7)
Fraction of inspired oxygen, median [IQR]	0.36 [0.27 – 0.50]	0.40 [0.27 – 0.50]
Oxygen saturation, median [IQR], %	96 [94–100]	95 [93 – 98]
Heart rate, median [IQR], beats per min	84 [78 – 109]	95 [78 – 102]
Mean arterial pressure, median [IQR]. mmHg	75 [67 – 80]	70 [66 – 76]
Vasopressors, No. (%)	9 (60.0)	9 (60.0)
Norepinephrine, median [IQR], mcg/min	8 [5 – 12]	8 [7 – 24]
Creatinine, median [IQR], mg/dL	1.6 [1.0 – 2.9]	0.9 [0.7 – 2.1]
Lowest in 12 months prior to hospitalization	0.9 [0.7 – 1.0]	1.0 [0.9 – 1.4]
Stage of acute kidney injury at enrollment †, No. (%)		
None	5 (33.3)	5 (33.3)
Stage I	1 (6.7)	4 (26.7)
Stage II	5 (33.3)	3 (20.0)
Stage III	4 (26.7)	3 (20.0)
APACHE II score, median [IQR]	29 [23 – 31]	24 [18 −30]
Fluid input in 24h prior to enrollment, median [IQR] mL	2,740 [441 – 4,599]	1,496 [325 – 2,448]

Baseline characteristics are compared between patients randomized to usual care versus conservative fluid management. IQR = interquartile range, ICU = intensive care unit, ARDS = acute respiratory distress syndrome, APACHE II = Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness

*Chronic kidney disease stage III or greater is defined as a glomerular filtration rate less than 60 ml/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation[32] using the patient's baseline creatinine value.

†Acute kidney injury is defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria[25].

Table 2.

Clinical Outcomes

Outcome	Usual Care (n = 15)	Conservative (n = 15)	*P* Value
Clinical Outcomes			
In-hospital mortality, No. (%)			
Before ICU discharge	2 (13.3)	2 (13.3)	>.99
Before hospital discharge	4 (26.7)	3 (30.0)	>.99
Support-free days to study day 14			
ICU-free days , median [IQR]	9 [0 – 12]	11 [0 – 12]	>.99
Ventilator-free days, median [IQR]	13 [0 – 14]	12 [0 −14]	.60
Vasopressor-free days, median [IQR]	13 [0 – 14]	12 [0 – 14]	.60
Renal replacement therapy-free days, median [IQR]	14 [0 – 14]	14 [14 – 14]	.36
Renal Outcomes			
Highest stage of acute kidney injury *, No. (%)			.28
None	5 (33.3)	6 (42.9)	
Stage I	0 (0.0)	2 (14.3)	
Stage II	4 (26.7)	3 (21.4)	
Stage III	6 (40.0)	3 (21.4)	
Plasma creatinine, mg/dL			
Highest after enrollment, median [IQR]	2.3 [1.1 – 3.1]	1.3 [.8 – 2.1]	.16
Change from baseline to highest value, median [IQR]	1.4 [0.1 – 2.2]	0.4 [0.0 – 1.3]	.18
Change from enrollment to highest value, median [IQR]	0.0 [−0.1 – 1.4]	-.03 [−0.1 – 0.7]	.95
Receipt of renal replacement therapy, No. (%)	1 (6.7)	1 (6.7)	>.99

ICU-free, ventilator-free, vasopressor-free, and renal replacement therapy free days refer to days alive and free from the specified therapy in the first 14 days after enrollment. ICU = intensive care unit, IQR = interquartile range

*Acute kidney injury is defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria[25].