Conservative Fluid Management after Sepsis Resuscitation: A Pilot Randomized Trial

Matthew W. Semler, MD, MSc; David R. Janz, MD, MSc; Jonathan D. Casey, MD; Wesley H. Self, MD, MPH; Todd W. Rice, MD, MSc

Online Data Supplement

Table of Contents

SUPPLEMENTAL METHODS 2
A. Study Definitions 2
B. Inclusion and Exclusion Criteria 4
C. Development of the Conservative Fluid Management Protocol 6
D. Conservative Fluid Management Protocol 7
E. Conservative Fluid Management Protocol Provided to the Bedside Nurse 12
SUPPLEMENTAL TABLES 13
Table E1. Sepsis evaluation and management prior to enrollment 13
Table E2. Fluid and diuretic interventions 15
Table E3. Composition of fluid input 16
Table E4. Hemodynamic and respiratory function 17
Table E5. Plasma laboratory values 18
Table E6. Radiographic assessment for acute respiratory distress syndrome 19
Table E7. Acute kidney injury 20
SUPPLEMENTAL REFERENCES 21

SUPPLEMENTAL METHODS

A. Study Definitions

"Study Day" – For the purposes of this study the term "study day" is defined as the 24 hour period beginning at 7am and ending at 7am the following day. Study day 0 will start at the time of enrollment and end at 7am the subsequent morning.

"Fluid Bolus" – For the purposes of this study the term "fluid bolus" will be defined as intravenous infusion of any crystalloid or colloid solution being administered to expand intravascular volume at a rate greater than or equal to 250ml/hour with a total volume of greater than or equal to 250ml.

"Maintenance Fluids" - For the purposes of this study the term "maintenance fluids" will be defined as intravenous infusion of any crystalloid solution being administered to maintain intravascular volume and replace insensible losses at a rate of less than or equal to 250ml/hour.

"Miscellaneous Fluids"

For the purposes of this study the term "miscellaneous fluids" will refer to intravenous fluid at any rate of any duration being administered in order to correct electrolyte abnormalities such as hypernatremia, hyponatremia, hyperglycemia, hypoglycemia, hypercalcemia; provide renal protection after contrast administration, during rhabdomyolysis, or during tumor lysis syndrome.

"Vasopressor Use" – For the purposes of this study "vasopressor use" will be defined as any continuous or intravenous infusion of epinephrine, norepinephrine, phenylephrine, dopamine, or vasopressin at any dose. Total dose of non-vasopressin vasopressors will be expressed in norepinephrine equivalents calculated by multiplying epinephrine dose by 1x and phenylephrine dose by 0.2x.

"Oliguria" – For the purposes of this study, "oliguria" will be defined as urine output < 0.5mL/kg/h for 6 hours or more.

"Acute Kidney Injury" – For the purposes of this study, "acute kidney injury" will be defined according to the KDIGO criteria[1]:

Stage I AKI

a. Serum creatinine increased by 1.5-1.9x baseline within 7 days, OR

b. Serum creatinine increased by ≥ 0.3mg/dL from baseline within 48 hours, OR

c. Urine output <0.5ml/kg/h for 6-12 hours

Stage II AKI

a. Serum creatinine increased by 2.0-2.9x baseline within 7 days, OR

b. Urine output < 0.5mL/kg/h for 12 or more hours.

Stage III AKI

a. Serum creatinine increased by ≥3.0x baseline within 7 days, OR

b. Serum creatinine increased to ≥ 4.0mg/dL, OR

c. Reduction in urine output to < 0.3mg/kg/hour for 24 hours or more, OR

d. Anuria for 12 hours or more, OR

e. Initiation of RRT

"Baseline Creatinine"

1. For patients with an available serum creatinine measurement within the last 12 months, the most recently recorded value will be used as their "baseline creatinine".

2. For patients without an available creatinine measurement within the last 12 months, the value for "baseline creatinine" will be the lower of the following:

a. lowest creatinine recorded in current admission prior to study enrollment, OR

b. creatinine estimated by the three-variable modified MDRD formula:

[Serum creatinine = 0.74−0.2(if female) + 0.08(if black) + 0.003 × age (in years)][2]

B. Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Admitted to the intensive care unit (ICU)
2. Age ≥ 18 years
3. Sepsis as defined by:
    a. At least two systemic inflammatory response syndrome (SIRS) criteria*, AND
    b. Presence of or suspicion for infection requiring antimicrobial therapy, AND
    c. Meeting the criterion #3a and #3b within a rolling 24 hour window.
4. Cardiopulmonary dysfunction as defined by ongoing:
    a. Shock
        i. Mean Arterial Pressure < 60 or vasopressor use; OR
    b. Respiratory Failure
        i. Invasive or Noninvasive Mechanical ventilation, OR
        ii. Oxygen Saturation < 97% on FiO2≥0.3

In order to be enrolled patients must meet criterion 3 and 4 within a 48 hour window. Cardiopulmonary dysfunction criteria must be met as a result of newly developed organ failure due to the acute septic process and not as a result of a chronic condition. All inclusion criteria must be met either at the study hospital or a referring hospital.

**Systemic Inflammatory Response Syndrome Criteria:*

1. *Hypothermia <36ºC or hyperthermia >38ºC*
2. *Heart rate (HR) >90 beats per minute*
3. *Respiratory rate (RR) >20 breaths/minute related to septic event, OR partial pressure of arterial carbon dioxide (PaCO2) <32 mmHg related to septic event, OR requiring mechanical ventilation related to septic event*
4. *Total WBC absolute count >12,000 cells/mm^3 or <4000 cells/mm^3.*

Exclusion Criteria:

1. Inability to obtain consent

2. Greater than 48 hours since inclusion criteria initially met
3. Allergy to furosemide AND bumetanide
4. Presence of the following active diagnoses:
    a. Rhabdomyolysis with creatinine kinase > 5000 U/L
    b. Hypercalcemia with calcium >11 mg/dL
    c. Diabetic Ketoacidosis requiring continuous insulin infusion
    d. Tumor Lysis Syndrome diagnosed clinically
    e. Pancreatitis diagnosed clinically
5. Presence of the following baseline comorbidities:
    a. Chronic Hypoxic Respiratory Failure with Home Oxygen Use of $FiO2 \geq 0.3$
    b. Chronic ventilator dependence
    c. Neuromuscular disease that may impair ventilator weaning
        i. cervical spinal cord injury at level C5 or higher
        ii. amyotrophic lateral sclerosis
        iii. Guillain-Barré Syndrome
        iv. myasthenia gravis
    d. Renal failure requiring renal replacement therapy
    e. Burns >20% of body surface area
    f. Pregnancy – pregnancy testing will be done as a part of standard of care, and participants who are capable of becoming pregnant but have not had pregnancy testing as a part of standard of care will be excluded from the study
    g. Preexisting pulmonary hypertension with PAP mean > 40 mmHg on RHC
    h. Severe chronic liver disease with Childs-Pugh Score >11
6. Moribund and not expected to survive an additional 24 hours
7. Actively withdrawing life support or transitioning to comfort measures only
8. Unwillingness of treating physician to employ conservative fluid strategy
9. Assessment of primary investigator, study staff, or treating physician that patient would not be a good study participant

C. Development of the Conservative Fluid Management Protocol

The conservative fluid management protocol used in this trial was adapted from 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[3,4]. The panel providing input during protocol development included:

- Gordon R. Bernard (Pulmonary and Critical Care Medicine);
- Arthur P. Wheeler (Pulmonary and Critical Care Medicine)
- Todd W. Rice (Pulmonary and Critical Care Medicine)
- Matthew W. Semler (Pulmonary and Critical Care Medicine)
- Lorraine B. Ware (Pulmonary and Critical Care Medicine)
- Liza Weavind (Anesthesia and Critical Care)
- David R. Janz (Pulmonary and Critical Care Medicine)
- Martha Reeves (Critical Care Nursing)
- Joanna L. Stollings (Critical Care Pharmacy)
- Jamie P. Dwyer (Nephrology)

D. Conservative Fluid Management Protocol

For patients randomized to the conservative fluid management strategy, a fluid management protocol dictated fluid receipt and removal from study initiation to termination. The fluid management protocol contained two components, the first of which determined fluid management in the presence of shock and the second when shock was absent.

Initiation of Conservative Fluid Management Strategy

As soon as the patient had been admitted to the study ICU for at least 12 hours and randomization had occurred, study staff notified nursing personnel of study group assignment and provided a written summary of the assigned intervention protocol including contact information of study staff. Treatment per study protocol was be initiated as follows:

- At initiation of the study protocol, all "maintenance" intravenous fluids were discontinued and were not to be resumed during the study period.
- At initiation of the study protocol, study staff requested that the clinical pharmacy maximally concentrate all intravenous medications for the duration of the study period.
- At initiation of the study, mean arterial pressure and vasopressor use in the prior 12 hours determined initial assignment to the "SHOCK" or "NOT in SHOCK" protocol group

Conservative Fluid Management Protocol Part 1: "SHOCK"

Patients who had experienced a MAP < 60 mmHg or vasopressor use in the prior 12 hours were considered to be in shock. For patients more than 12 hours from admission to the study ICU and in shock, fluid boluses were NOT administered except as directed by the protocol for the indications of oliguria and worsening shock. MAP 60 – 80 mmHg was maintained using addition of or titration of vasopressors (***).

Oliguria: If a patient in shock experienced a urine output of less than 30 mL/h for at least 6 hours, a fluid bolus of 500 mL of crystalloid was administered over 30 minutes. If urine output was more than 30 mL/h in the following two hours, the patient returned to the study protocol of fluid restriction and vasopressor titration and did not receive further fluid boluses at that time. If urine output was less than 30 mL/h in the following two hours, a fluid bolus of an additional 1,000 mL of crystalloid was administered after which the patient returned to the study protocol

of fluid restriction and vasopressor titration. If a patient previously treated with a fluid bolus for oliguria experienced another 6 hour period of oliguria, the fluid boluses were repeated as per the protocol to a maximum of 3 L of crystalloid administered in fluid boluses on a given study day. In a patient who experiences urine output < 30 mL/h for 24 hours, the protocol was held until urine output ≥ 30 mL/h for 6 consecutive hours and then resumed. In a patient who was started on renal replacement therapy, the protocol was held until the study day following the final episode of renal replacement therapy.

Worsening Shock: If a patient in shock experienced increasing vasopressor requirements, the administration of IV fluid boluses and vasopressor administration was dictated by the study protocol. For patients requiring less than 10 mcg/min of norepinephrine (or equivalent), fluid boluses were not administered. For patients whose norepinephrine rate was greater than or equal to 10 mcg/min and whose rate had increased by more than 5 mcg/min in the prior six hours, a fluid bolus of 500 mL of crystalloid was administered over 30 minutes and then fluid restriction and vasopressor titration through the protocol was resumed. For patients whose norepinephrine dose was greater than or equal to 20 mcg/min and whose vasopressor requirement had increased more than 10 mcg/min in the last 6 hours, a fluid bolus of 500 mL over 30 minutes was administered and then fluid restriction and vasopressor titration through the protocol was resumed. If a patient who had previously received a fluid bolus for worsening shock again met criteria by vasopressor increase over another 6 hour period, another fluid bolus was administered in accordance with the study protocol to a maximum of 3 L of IV fluid bolus intake on a given study day. In patients whose vasopressor requirement equaled or exceeded 60 mcg/min or had increased more than 20 mcg/min in the last 6 hours, the protocol was held until the patient's mean arterial pressure was stable in the goal range for six hours without addition of or increased dose of vasopressors.

Fluid Bolus Administration: In patients on study in shock, fluid boluses were only administered as directed by the study protocol for oliguria or worsening shock. When a fluid bolus was indicated in accordance with the protocol, the fluid bolus volume was determined by the protocol and the type of crystalloid to be administered was determined by the treating clinician. Fluid boluses were administered over 30 minutes and vital signs and urine output were measured and recorded before and after each fluid bolus. The maximum volume of fluid which was given in the form of protocol-directed fluid boluses on a given study day was 3 L. *If a fluid*

bolus was indicated by the study protocol but the treating clinicians felt administering a fluid bolus would be unsafe, the fluid bolus was NOT administered.

Acute Event: If a patient experienced a cardiac arrest, post-intubation hypotension, or hemodynamically significant bleeding, the nurse notified the clinical team and study staff and the protocol was held until the mean arterial pressure was in the goal range for 6 consecutive hours without addition of or increased dose of vasopressors.

Resolution of Shock: If a patient who had been in shock achieved MAP ≥ 60 mmHg for 12 hours without the use of vasopressors, the protocol transitioned to "NOT in SHOCK".

Conservative Fluid Management Protocol Part 2: "NOT in SHOCK"

Patients who had not experienced a MAP < 60 mmHg or vasopressor use in the prior 12 hours were considered not to be in shock. For patients who had been in the study ICU for more than 12 hours and who were not in shock, (1) fluid boluses were not administered except as directed by the protocol for oliguria and (2) a fluid balance of total output greater than total input was targeted for each 24 hour period utilizing a diuretic infusion if necessary (Figure 2).

Oliguria: If a patient not in shock experienced a urine output of less than 30 mL/h for 6 hours, the diuretic infusion was discontinued and a fluid bolus of 500 mL of crystalloid was administered over 30 minutes. If urine output was more than 30 mL/h in the following two hours, no further fluid was administered and the diuretic infusion was restarted after urine output was more than 30 mL/h for 6 hours. If urine output was less than 30 mL/h in the following two hours, a fluid bolus of 1000 mL of crystalloid was administered and the diuretic infusion was restarted after the urine output was more than 30 mL/h for 6 hours. If, after receiving a fluid bolus, a patient again experienced urine output of less than 30 mL/h for 6 hours, the protocol was repeated up to a maximum of 3 L of intravenous fluid boluses directed by the protocol on a given study day. In a patient who experienced urine output < 30 mL/h for 24 hours, the protocol was held until urine output ≥ 30 mL/h for 6 consecutive hours and then was resumed. In a patient who was started on renal replacement therapy, the protocol was held until the study day following the final episode of renal replacement therapy.

Fluid Bolus Administration: In patients on study not in shock, fluid boluses were only administered as directed by the study protocol for oliguria. If a fluid bolus was directed by the protocol, the specified volume of whichever crystalloid was preferred by the treating clinician

was administered. The fluid bolus was administered over 30 minutes and vital signs and urine output were measured and recorded before and after the fluid bolus. The maximum volume of fluid which was given in the form of protocol-directed fluid boluses on a given study day was 3 L. *If a fluid bolus was indicated by the study protocol but the treating clinicians felt administering a fluid bolus would be unsafe, the fluid bolus was NOT administered.*

New Shock: If mean arterial pressure < 60 mmHg or vasopressor use developed, the nurse notified the clinical team and study staff and the protocol was resumed in "SHOCK".

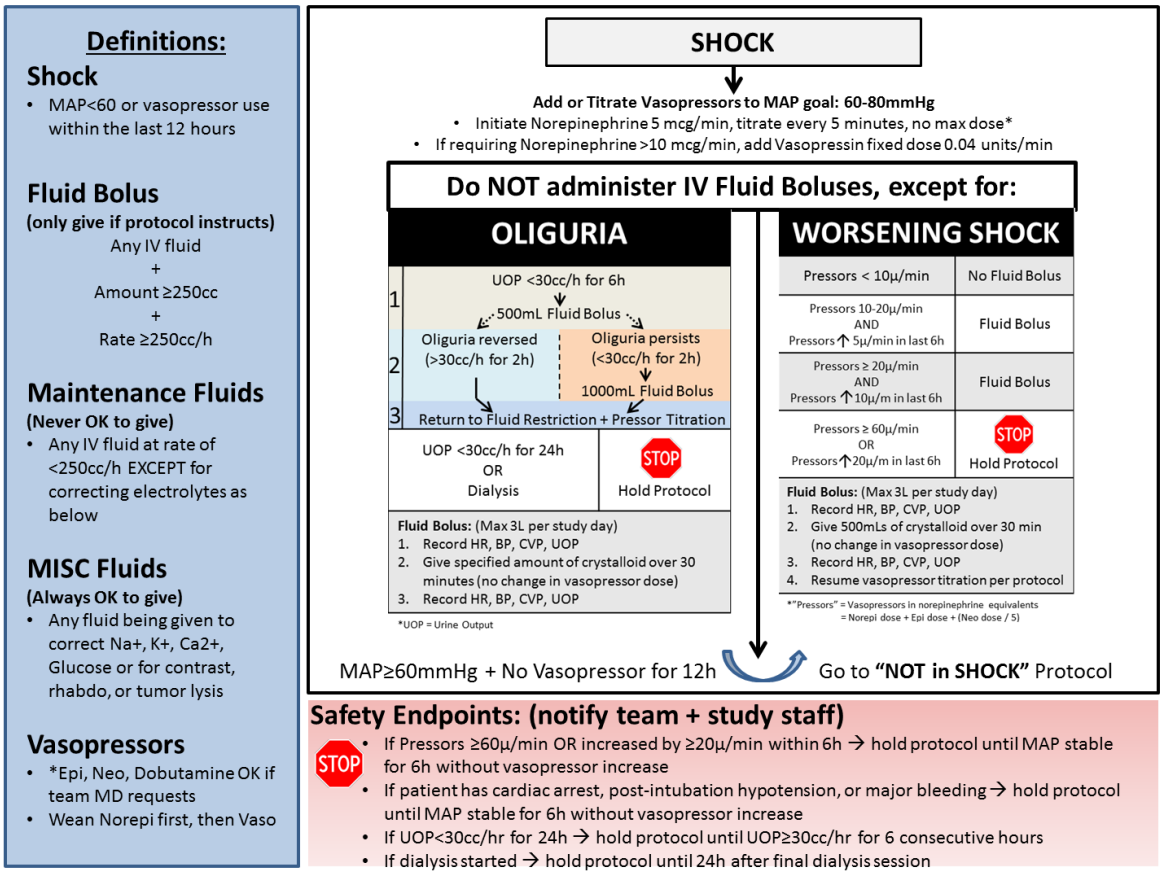
Diuretic Infusion: For patients not in shock, nursing personnel initiated a continuous intravenous infusion of loop diuretic without a loading dose. If furosemide was clinically available and the patient was not allergic, the diuretic infusion was furosemide beginning at 3 mg/h titrated as needed up to a maximum of 24 mg/h. If the patient was allergic to furosemide OR furosemide was clinically unavailable, the diuretic infusion was bumetanide beginning at 0.1 mg/h titrated as needed to a maximum dose of 0.6 mg/h. For patients previously receiving infusion in whom infusion was held for development of shock or oliguria, it was re-started at half the prior dose. For patients previously receiving infusion in whom it was held for another indication, the infusion was restarted at the prior dose. For the first 4 hours after initiation or re-initiation, total fluid input, total fluid output, and urine output was assessed hourly and if fluid input exceeds output in a given hour the rate of infusion was doubled up to a maximum of 24 mg/h. Subsequently, at least every four hours during the infusion, nursing personnel measured and documented fluid intake, fluid output, and urine output.

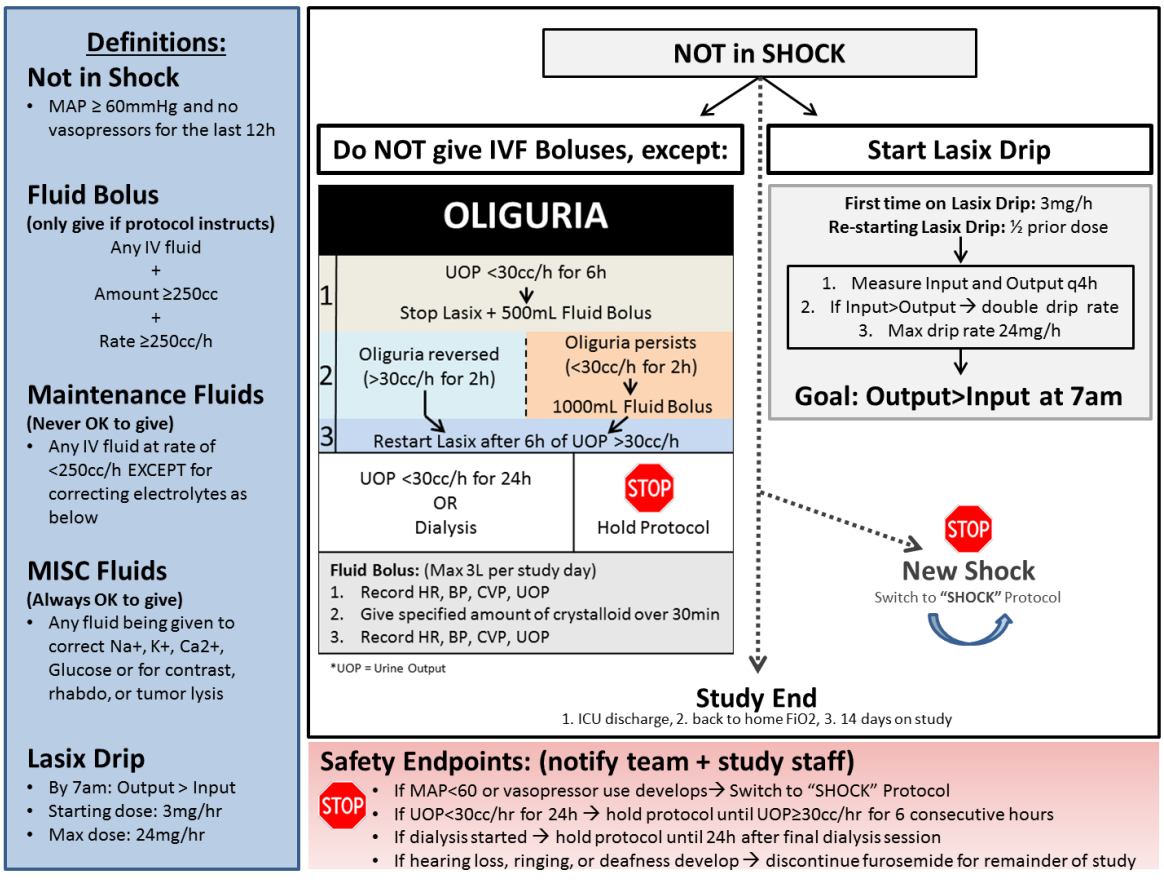
The primary objective was a total output greater than input for a given study day (ie "net negative" for a 24h period beginning and ending at 7am). To achieve this, nursing personnel utilized fluid input and output measures from each 4 hour period and the prior periods that day to adjust the diuretic infusion to target fluid balance. In general, if fluid input exceeded output by ≥ 150 mL in a 4 hour period or cumulative fluid input exceeded output by ≥ 500 mL at any point during the study day, the dose of diuretic infusion was doubled until target achieved or until maximum infusion rate of 24mg/hour was reached. If fluid output exceeded input by ≥150 mL in a 4 hour period AND cumulative fluid output exceeds fluid input by ≥1000 mL for the day, the dose of diuretic infusion was halved until target achieved or until diuretic infusion was held for continued output exceeding input at a diuretic infusion rate less than then initial starting dose.

Compliance with the protocol was not based on adjustments made at each 4 hour interval but instead based on the 24 hour target net fluid balance.

If it was the intent of the clinical team for a patient to have net fluid output exceed net input by a specific amount on a given study day, additional diuretic was allowed to achieve the clinical team's fluid balance goal up to a maximum hourly diuretic dose proscribed by the study.

E. Conservative Fluid Management Protocol Provided to the Bedside Nurse





SUPPLEMENTAL TABLES

Table E1. Sepsis evaluation and management prior to enrollment

Characteristic	Usual Care (n = 15)	Conservative (n = 15)
SIRS criteria met, No (%)		
Temperature > 38 degrees	6 (40.0)	9 (60.0)
Temperature < 36 degrees	1 (6.7)	0 (0.0)
Heart rate > 90 beats/min	14 (93.3)	14 (93.3)
Respiratory rate > 20 breaths/min	12 (80.0)	15 (100.0)
White blood cell count > 12	8 (53.3)	14 (93.3)
White blood cell count < 4	1 (6.7)	0 (0.0)
Cardiopulmonary dysfunction criteria met, No (%)		
Mean arterial pressure < 60 or vasopressor use	9 (60.0)	9 (60.0)
Mechanical ventilation	7 (46.7)	8 (53.3)
Oxygen saturation < 97% on FiO_2 > 0.3	8 (53.3)	9 (60.0)
Shock present at time of randomization, No (%)	9 (60.0)	9 (60.0)
Time, median [IQR]		
Study ICU admission to enrollment*, hours	12.5 [9.2 – 15.8]	14.4 [8.1 – 22.2]
Enrollment to randomization†, min	3.0 [2.0 – 171.0]	4.0 [2.0 – 212.0]
Randomization to protocol initiation‡, min	--	2.0 [1.0 – 3.0]
24 hours prior to enrollment		
Fluid input, median [IQR] mL	2,740 [441 – 4,599]	1,496 [325 – 2,448]
Urine output, median [IQR], mL	675 [180 – 1,260]	1,400 [325 – 2,147]
Antibiotic administration, No (%)	15 (100.0)	15 (100.0)
Lactic acid, median [IQR], mg/dL	1.0 [0.9 – 1.8]	2.2 [1.0 – 3.9]
Ultrasound at enrollment		
IVC maximum diameter, median [IQR], cm	1.2 [1.0 – 1.6]	1.5 [1.0 – 2.0]
IVC minimum diameter, median [IQR], cm	0.8 [0.7 – 1.0]	0.9 [0.3 – 1.2]

Sepsis evaluation and management prior to study enrollment is compared between the usual care and conservative fluid management groups. SIRS = systemic inflammatory response syndrome, IQR = interquartile range, ICU = intensive care unit, IVC = inferior vena cava

*Enrollment occurred at the time informed consent was signed.

†Randomization occurred immediately after enrollment for patients who had already been in the study ICU for at least 12 hours. For patients who were enrolled within 12 hours of admission to the study ICU, randomization was delayed until 12 hours after ICU admission.

‡For patients in the conservative fluid management group, the conservative fluid management protocol was initiated as soon as possible after randomization.

Table E2. Fluid and diuretic interventions

Intervention Characteristics	Usual Care (n = 15)	Conservative (n = 15)	*P* Value
Time from enrollment to study termination, median [IQR], hours	70 [26 – 77]	50 [27 -121]	.65
Indication for study termination, No. (%)			
ICU transfer	12 (80.0)	9 (60.0)	.33
Cessation of vasopressors and return to baseline FiO_2	1 (6.7)	4 (26.7)	
Death	2 (13.3)	2 (13.3)	
14 days after enrollment	0 (0.0)	0 (0.0)	
Interventions received during the study			
Number of IV fluid boluses, No. (%)			.35
Zero	9 (60.0)	11 (73.3)	
One	1 (6.7)	1 (6.7)	
Two	3 (20.0)	2 (13.3)	
Three	1 (6.7)	1 (6.7)	
Four	1 (6.7)	0 (0.0)	
Total volume of IV fluid as boluses, mean ± SD, mL	733 ± 1,083	300 ± 560	.30
Maintenance IV fluid*, No. (%)	4 (26.7)	3 (20.0)	>.99
Total dose of loop diuretic received			
Furosemide, mean ± SD, mg	33 ± 68	133 ± 361	.34
Torsemide, mean ± SD, mg	8 ± 31	32 ± 124	.96
Bumetanide, mean ± SD, mg	0 ± 0	0 ± 0	>.99
Receipt of continuous loop diuretic infusion, No. (%)	0 (0)	6 (40.0)	.02
Days receiving loop diuretic infusion, mean ± SD	0 ± 0	0.9 ± 1.6	.007
Non-loop diuretic, No. (%)	1 (6.7)	0 (0)	>.99

Fluid and diuretic administration is compared between the usual care and conservative fluid management groups. IQR = interquartile range, IV = intravenous, SD = standard deviation

*Maintenance IV fluid was received by 3 patients in the conservative fluid management group between enrollment and randomization. No patients in the conservative fluid management group received maintenance IV fluid after randomization.

Table E3. Composition of fluid input

Fluid Input	Usual Care (n = 15)	Conservative (n = 15)	*P* value
Cumulative volume day 0 to 14, mean ± SD, mL			
0.9% sodium chloride	483 ± 811	398 ± 745	.76
Lactated Ringer's	357 ± 798	339 ± 621	.74
Hypotonic crystalloid	133 ± 516	63 ± 187	.61
5% dextrose in water	210 ± 655	127 ± 491	.55
5% dextrose with bicarbonate	0 ± 0	73 ± 284	.32
Enteral nutrition	2,269 ± 2,119	2,288 ± 2,233	.93
Enteral free water	786 ± 2,494	1,787 ± 5,093	.44
IV medications	2,438 ± 1,984	3,310 ± 3,282	.82
Packed red blood cell transfusion	45 ± 119	163 ± 320	.29
Fresh frozen plasma transfusion	84 ± 328	14 ± 56	.96
Platelet transfusion	59 ± 228	19 ± 75	.96

Volume and composition of fluid input during the study is compared between the usual care and conservative fluid management groups. No patient in either group received any volume of parenteral nutrition, Plasmalyte A, 3% sodium chloride, 5% or 25% human serum albumin, or any semi-synthetic colloid solution. SD = standard deviation, IV = intravenous

Table E4. Hemodynamic and respiratory function

Physiologic variable	Usual Care (n = 15)	Conservative (n = 15)	*P* Value
Highest heart rate, median [IQR], beats/min			
Day 0 (n = 30)	104 [89 – 128]	116 [103 – 126]	.49
Day 1 (n = 26)	95 [91 – 122]	105 [99 – 123]	.57
Day 2 (n = 17)	95 [90 – 106]	108 [90 – 127]	.34
Day 3 (n =12)	97 [87 – 119]	121 [101 – 130]	.17
Lowest systolic blood pressure, median [IQR], mmHg			
Day 0 (n = 30)	89 [83 – 96]	88 [82 – 93]	.79
Day 1 (n = 26)	95 [86 – 106]	94 [88 – 98]	.68
Day 2 (n = 17)	103 [94 – 108]	91 [87 – 104]	.19
Day 3 (n =12)	121 [100 – 124]	90 [86 – 94]	.07
Lowest mean arterial pressure, median [IQR], mmHg			
Day 0 (n = 30)	57 [53 – 62]	57 [53 – 60]	.71
Day 1 (n = 26)	60 [53 – 66]	61 [59 – 63]	.78
Day 2 (n = 17)	66 [59 – 70]	62 [58 – 64]	.41
Day 3 (n =12)	72 [64 – 81]	63 [63 – 65]	.11
Vasopressor use, No. (%)			
Day 0 (n = 30)	9 (60.0)	10 (66.7)	>.99
Day 1 (n = 26)	5 (38.5)	5 (38.5)	>.99
Day 2 (n = 17)	4 (55.6)	4 (50.0)	>.99
Day 3 (n =12)	0 (0.0)	2 (40.0)	.15
Lowest oxygen saturation, median [IQR], %			
Day 0 (n = 30)	90 [89 – 93]	90 [88 – 92]	.60
Day 1 (n = 26)	90 [88 – 93]	90 [88 - 92]	.74
Day 2 (n = 17)	90 [84 – 92]	92 [90 – 94]	.36
Day 3 (n =12)	90 [88 – 91]	93 [92 – 96]	.15
Highest FiO_2, median [IQR]			
Day 0 (n = 30)	0.40 [0.27 – 0.50]	0.50 [0.30 – 0.70]	.24
Day 1 (n = 26)	0.39 [0.27 – 0.50]	0.40 [0.33 – 0.60]	.52
Day 2 (n = 17)	0.45 [0.27 – 0.50]	0.40 [0.30 – 0.78]	>.99
Day 3 (n =12)	0.30 [0.27 – 0.51]	0.39 [0.39 – 0.40]	.88
Lowest SpO_2/FiO_2 ratio, median [IQR]			
Day 0 (n = 30)	232 [190 – 348]	198 [132 – 300]	.21
Day 1 (n = 26)	244 [178 – 329]	225 [160 – 272]	.51
Day 2 (n = 17)	217 [182 – 333]	233 [125 – 303]	.96
Day 3 (n =12)	348 [176 – 362]	234 [188 – 241]	.41

Hemodynamic and respiratory function is compared between the usual care and conservative fluid management groups. IQR = interquartile range, FiO_2 = fraction of inspired oxygen, SpO_2 = arterial oxygen saturation

Table E5. Plasma laboratory values

Laboratory value	Usual Care (n = 15)	Conservative (n = 15)	*P* Value
Sodium, median [IQR], mmol/L			
Enrollment (n = 30)	136 [133 – 139]	135 [133 – 140]	.95
Day 1 (n = 26)	137 [135 – 140]	139 [134 – 140]	.88
Day 2 (n = 17)	138 [137 – 141]	139 [137 – 142]	.65
Day 3 (n =12)	140 [137 – 143]	138 [136 – 142]	.41
Potassium, median [IQR], mmol/L			
Enrollment (n = 30)	4.2 [4.0 – 5.3]	4.1 [3.5 – 4.3]	.06
Day 1 (n = 26)	3.9 [3.7 – 4.5]	3.7 [3.4 – 4.2]	.11
Day 2 (n = 17)	3.8 [3.3 – 4.4]	3.9 [3.7 – 4.4]	.76
Day 3 (n =12)	3.5 [3.4 – 3.8]	3.9 [3.6 – 4.2]	.15
Chloride, median [IQR], mmol/L			
Enrollment (n = 30)	105 [102 – 109]	106 [101 – 109]	.78
Day 1 (n = 26)	104 [102 – 109]	106 [101 – 109]	.75
Day 2 (n = 17)	103 [102 – 107]	104 [102 – 107]	>.99
Day 3 (n =12)	104 [103 – 107]	104 [100 – 105]	.68
Bicarbonate, median [IQR], mmol/L			
Enrollment (n = 30)	17 [15 – 20]	19 [16 -23]	.23
Day 1 (n = 26)	19 [17 – 23]	22 [18 – 25]	.38
Day 2 (n = 17)	22 [18 – 25]	22 [19 – 28]	.76
Day 3 (n =12)	25 [19 – 26]	27 [22 -29]	.76
Blood urea nitrogen, median [IQR], mg/dL			
Enrollment (n = 30)	39 [16 – 56]	20 [14 – 40]	.17
Day 1 (n = 26)	39 [21 – 58]	22 [13 – 38]	.05
Day 2 (n = 17)	34 [23 – 47]	20 [8 – 35]	.12
Day 3 (n =12)	25 [19 – 26]	27 [22 – 29]	.20
Creatinine, median [IQR], mg/dL			
Enrollment (n = 30)	1.6 [1.0 – 2.9]	0.9 [0.7 – 2.1]	.19
Day 1 (n = 26)	1.3 [1.1 – 2.7]	0.9 [0.7 – 2.1]	.11
Day 2 (n = 17)	1.4 [0.8 – 2.7]	0.9 [0.7 – 1.6]	.32
Day 3 (n =12)	0.9 [0.7 – 2.6]	0.8 [0.6 – 1.2]	.76
Adjusted Creatinine, median [IQR], mg/dL*			
Day 1 (n = 26)	1.3 [1.1 – 2.7]	0.9 [0.7 – 1.6]	.10
Day 2 (n = 17)	1.4 [0.8 – 3.0]	0.9 [0.6 – 1.6]	.37
Day 3 (n =12)	0.9 [0.6 – 3.1]	0.8 [0.6 – 1.1]	.81

Plasma laboratory values are compared between the usual care and conservative fluid management groups. IQR = interquartile range. * Adjusted Cr = SCr*(1+[cumulative net fluid balance/total body water]) in which SCr is measured serum creatinine and total body water is 0.6 * patient weight at randomization.

Table E6. Radiographic assessment for acute respiratory distress syndrome

	Usual Care (n = 15)	Conservative (n = 15)	*P* Value
Chest radiography consistent with ARDS, No. (%)			
At enrollment	5 (33.3%)	7 (46.7%)	.46
On any study day 1-14	7 (46.7%)	6 (40.0%)	.71
Developed between enrollment study day 14	3 (20.0%)	1 (6.7%)	.28
Ever present, enrollment through study day 14	8 (53.3%)	8 (53.3%)	>.99

Chest radiography from enrollment and study days 1-14 were reviewed for meeting radiographic criteria for acute respiratory distress syndrome [5] independently by two pulmonary and critical care medicine physicians blinded to study group assignment. Inter-rater agreement was moderate to good (kappa = 0.61; $P < .001$). Discrepancies between the initial two reviewers were resolved by independent review by a third, blinded, pulmonary and critical care medicine physician.

ARDS = acute respiratory distress syndrome

Table E7. Acute kidney injury

	Usual Care	Conservative	*P* Value
Highest stage of AKI, No.			
Enrollment	(n = 15)	(n = 15)	.54
None	5	5	
Stage I	1	4	
Stage II	5	3	
Stage III	4	3	
Day 0	(n = 15)	(n = 14)	.04
None	5	9	
Stage I	0	2	
Stage II	4	1	
Stage III	6	2	
Day 1	(n = 12)	(n = 11)	.87
None	7	5	
Stage I	1	3	
Stage II	2	1	
Stage III	2	2	
Day 2	(n = 7)	(n = 8)	.70
None	4	5	
Stage I	1	0	
Stage II	1	0	
Stage III	1	3	
Day 3	(n = 7)	(n = 5)	.40
None	5	3	
Stage I	2	0	
Stage II	0	2	
Stage III	0	2	
Highest stage of AKI between enrollment and day 14, No. (%)	(n=15)	(n=15)	.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)	

The incidence of acute kidney injury is compared between the usual care and conservative fluid management groups. AKI = acute kidney injury

SUPPLEMENTAL REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter. 2012;2(Suppl):8.

2. Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2010;25:3911–8.

3. Grissom CK, Hirshberg EL, Dickerson JB, Brown SM, Lanspa MJ, Liu KD, et al. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome*. Crit Care Med. 2015;43:288–95.

4. Huang DT, Angus DC, Moss M, Thompson BT, Ferguson ND, Ginde A, et al. Design and Rationale of the Reevaluation of Systemic Early Neuromuscular Blockade Trial for Acute Respiratory Distress Syndrome. Ann Am Thorac Soc. 2017;14:124–33.

5. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA J Am Med Assoc. 2012;307:2526–33.