CHEST

Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock

A Pilot Study

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BACKGROUND: IV fluid represents a basic therapeutic intervention for septic shock. Unfortunately, the optimal administration of IV fluid to maximize patient outcomes and prevent complications is largely unknown.

METHODS: Patients with septic shock admitted to the medical ICUs of Barnes-Jewish Hospital (January to December 2014) requiring vasoactive agents for at least 12 h following initial fluid resuscitation were randomized to usual care or to targeted fluid minimization (TFM) guided by daily assessments of fluid responsiveness.

RESULTS: Eighty-two patients were enrolled, 41 to usual care and 41 to TFM. For patients randomized to TFM, the net median (interquartile range) fluid balance was less at the end of day 3 (1,952 mL [48-5,003 mL] vs 3,124 mL [767-10,103 mL], $P = .20$) and at the end of day 5 (2,641 mL [−1,837 to 5,075 mL] vs 3,616 mL [−1,513 mL to 9,746 mL], $P = .40$). TFM appeared to be safe, as indicated by similar clinical outcomes including in-hospital mortality (56.1% vs 48.8%, $P = .51$), ventilator days (8.0 days [3.25-15.25 days] vs 5.0 days [3.0-9.0 days], $P = .30$), renal replacement therapy (41.5% vs 39.0%, $P = .82$), and vasopressor days (4.0 days [2.0-8.0 days] vs 4.0 days [2.0-6.0 days], $P = .84$).

CONCLUSIONS: This pilot study suggests that TFM in patients with septic shock can be performed using protocol-guided assessments of fluid responsiveness. Larger trials of TFM in septic shock are needed.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02473718; URL: www.clinicaltrials.gov

CHEST 2015; 148(6):1462-1469

Manuscript received June 25, 2015; revision accepted July 31, 2015; originally published Online First August 20, 2015.

ABBREVIATIONS: EVLW = extravascular lung water; IVC = inferior vena cava; IVF = IV fluid; TFM = targeted fluid minimization

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: 10.1378/chest.15-1525

Since Rivers et al[1] demonstrated in 2001 that early goal-directed therapy improved survival in patients with septic shock, fluid resuscitation has become a mainstay for the treatment of severe sepsis and septic shock.[2] However, there is a growing body of evidence suggesting that an excessively positive fluid balance is associated with worse outcomes in ARDS,[3-5] acute renal failure,[6,7] and septic shock.[8,9] Moreover, recent prospective, randomized controlled trials have questioned the efficacy of early goal-directed therapy, because no mortality benefit was demonstrated in the Australasian Resuscitation in Sepsis Evaluation (ARISE), Protocolized Care for Early Septic Shock (ProCESS), or Protocolised Management in Sepsis (ProMISE) trials.[10-12] Although studies have been performed demonstrating no mortality benefit and possible harm with the use of dobutamine and excessive RBC transfusions in severe sepsis and septic shock,[13-15] there are no prospective, randomized controlled trials examining the role of targeted fluid minimization (TFM) following initial fluid resuscitation in septic shock.

Given the growing body of evidence that excessive fluid administration may be harmful in septic shock,[16] there has been renewed interest in predicting fluid responsiveness. Static measures, such as central venous pressure and central venous oxygen saturation, have been shown previously to be poor predictors of fluid responsiveness.[17,18] Dynamic measures, such as pulse pressure variation and inferior vena cava (IVC) distension, have shown more promise, but only under controlled situations (ie, passive positive pressure breathing with 8-10 mL/kg ideal body weight tidal volumes).[19] We hypothesized that a protocol of daily fluid status assessment resulting in TFM could be used safely in patients with septic shock deemed not to be volume responsive. Therefore, we performed a pilot study to determine the feasibility of testing the aforementioned hypothesis in patients with septic shock.

Materials and Methods

Approval of Study Design

This prospective, randomized study was approved by the institutional review board for human research at Washington University. It was conducted under the auspices of an independent safety, efficacy, and data monitoring committee (HRPO number 201503035).

Eligibility

Eligible adult patients with septic shock who presented to the medical ICU of a 1,250-bed academic tertiary care hospital from January 2014 through December 2014 were assessed for possible enrollment according to the inclusion and exclusion criteria. The criteria for inclusion were septic shock as the primary cause of hypotension and hypotension necessitating vasoactive drugs that persisted for at least 12 h after initial adequate IV fluid (IVF) administration and at the time of enrollment. Initial adequate IVF administration was defined as the administration of at least 30 mL/kg ideal body weight of normal saline or lactated Ringer solution. The criteria for exclusion from the study were prior enrollment in the study, age $<$18 years, presence of end-stage renal disease necessitating hemodialysis or peritoneal dialysis as an outpatient immediately prior to admission, pregnancy, or goals of care consistent with comfort measures only. Written informed consent was obtained from the patient when able, and if the patient was unable to provide consent, then consent was obtained from the patient's legal representative.

Study Protocol

After informed consent, patients were stratified based on the presence or absence of ARDS, then randomized to either standard (control) therapy or TFM therapy (Fig 1). Baseline parameters, including central venous pressure, mean arterial pressure, central venous oxygen saturation, pulse pressure variation, and inspiratory and expiratory IVC diameters were obtained for all patients. Stroke volume and cardiac output were also measured, using transesophageal Doppler (CardioQ; Deltex Medical) in intubated patients and transthoracic Doppler (USCOM) in nonintubated patients. Following measurement of baseline parameters in the TFM therapy group, a fluid challenge was performed by passive leg raise, or, if the primary team had already decided to administer a fluid bolus or perform an RBC transfusion, this was used in lieu of a passive leg raise. Following passive leg raise or fluid administration, parameters were repeated and fluid responsiveness was assessed. Patients were considered fluid responsive if the pulse pressure variability decreased to $<$13%, the IVC distension index decreased to $<$18%, and the stroke volume index difference increased by $>$10%.[19-21] At least two of these parameters had to be met to be considered fluid responsive. In the standard therapy group, the baseline hemodynamic data were obtained and made available to the treating medical team without data interpretation. All tests were performed and interpreted by one investigator (C. C.), and pulse pressure variation was measured only if the patient had an arterial line placed by their treating physician team.

All assessment results for patients assigned to TFM therapy were discussed directly with the primary medical team. In patients who were deemed to be fluid responsive, recommendations to continue IVF administration were made using 500 mL boluses of normal saline or lactated Ringer solution until fluid responsiveness could no longer be demonstrated. In patients who were deemed to not be fluid responsive, TFM therapy was initiated: Continuous therapeutic infusions were concentrated, maintenance IVFs were discontinued, carrier fluids were minimized, and the use of diuretic therapy or fluid removal with renal replacement therapy was discussed and encouraged with the primary team based on the patient's renal function.

Fluid responsiveness parameters were repeated daily for 5 days or until the patient was discharged from the ICU or died. In addition to the fluid responsiveness parameters, daily fluid intake and output were assessed. The APACHE (Acute Physiology and Chronic Health Evaluation) II and Sequential Organ Failure Assessment (SOFA) scores were calculated for all patients at the time of enrollment in the study. Comorbidities, including systolic and diastolic heart failure, chronic kidney disease, active malignancy, and end-stage liver disease, were also recorded.

Outcomes

The primary outcome for this pilot study was the volume of study fluids administered by days 3 and 5 and the cumulative fluid balance by days 3 and 5. Study fluids were defined as colloid and crystalloid boluses and all continuous infusions administered from study enrollment through day 5. Secondary outcomes included the frequency of renal replacement therapy, maximal vasopressor dose in μg/min, number of days requiring vasopressor use, number of vasopressor-free days, mean arterial pressure during the enrollment period, number of ventilator days, number of ventilator-free days, and in-hospital mortality.

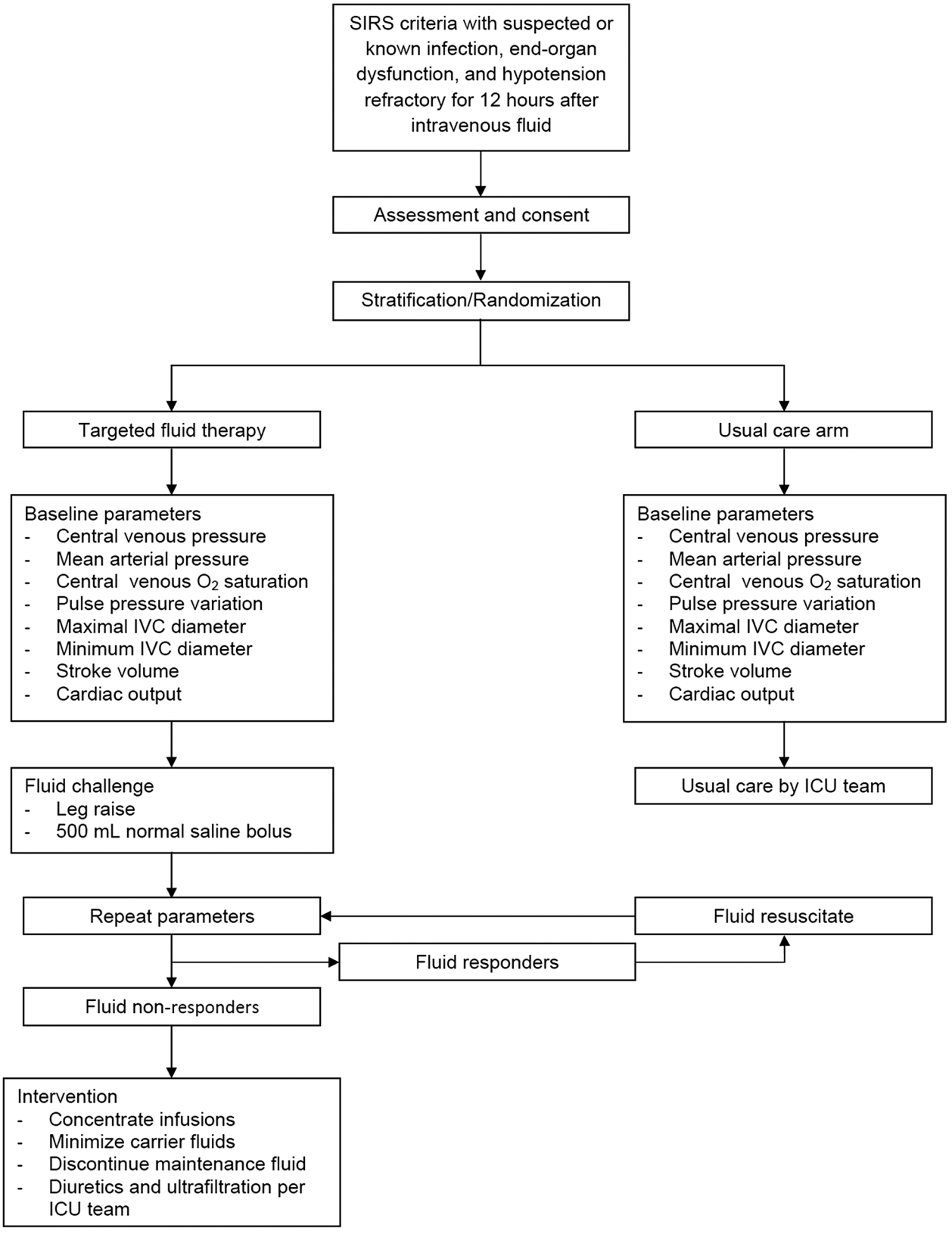

Figure 1 – *Study protocol for patients assigned to targeted fluid minimization therapy and to usual care. IVC = inferior vena cava; SIRS = systemic inflammatory response syndrome.*

Statistical Analysis

To determine sample size, a power analysis was performed assuming that the control arm would have a cumulative IVF intake of 7,000 mL and the intervention arm would have a cumulative IVF intake of 4,500 mL by day 3. Assuming a rate of refusal of 10% and a power of 80%, a sample size of 45 participants in each arm was calculated. Primary analysis was by intention to treat. The Student *t* test was used when comparing normally distributed data and the Mann-Whitney *U* test was used to analyze nonnormally distributed data. Categorical data were expressed as frequency distributions and the χ^2 test or Fisher exact test for small samples was used to determine whether differences existed between groups. All tests were two tailed, and a *P* value $< .05$ was determined to represent statistical significance. Analyses were performed using SPSS, version 11.0 for Windows (IBM Corporation).

Results

Two hundred seventy-three patients met the inclusion criteria for this pilot study. Eighty patients met the exclusion criteria (Fig 2). Four patients died or were transferred to another service prior to consent being obtained. Eleven patients refused enrollment. Ninety-six patients who met the inclusion criteria and did not meet the exclusion criteria were unable to provide consent, and their legal representative could not be identified or reached. The remaining 82 patients were enrolled in the study, 41 in each arm.

Thirty-one patients in the intervention arm (75.6%) had fluid responsiveness assessed using the IVC distension index and the stroke volume index, with 10 (24.4%) having all three assessments (stroke volume index, IVC distension, pulse pressure variability) performed. For patients in the control arm, 35 (85.4%) had baseline measurements of the IVC distension index and the stroke volume index, with six (14.6%) having all three baseline measurements performed. Five patients in the intervention arm did not reach any primary end points because of death. Three patients in the control arm did not reach any primary end points: Two died, and one was discharged home on hospice. Thirty-six patients in the intervention arm and 38 patients in the control arm completed at least 3 days of the study protocol and reached at least one primary end point. Five additional patients in the intervention arm did not complete the 5-day enrollment period: three because of discharge from the ICU and two because of death. Seven additional patients in the control arm did not complete the 5-day enrollment period: five because of discharge and two because of death. Thirty-one patients in the intervention arm and 31 patients in the control arm completed the 5-day enrollment period. None were lost to follow-up.

There was no statistically significant difference between the intervention and the control arms in age, BMI, severity of illness scores, or frequency of intubation (Table 1). There was no statistically significant difference between the intervention and control arms in the underlying comorbidities examined, although there was a trend toward a greater prevalence of active malignancy and end-stage liver disease in the intervention arm. Table 2 shows that 13 patients (31.7%) in the intervention arm were fluid responsive on study day 1, with decreasing fluid responsiveness observed on study days 2 through 5. Fluid nonresponders were managed primarily with concentration and/or elimination of their IVFs followed by fluid removal, with renal replacement therapy or diuretic therapy depending on the patient's renal function. On study day 1, there was no difference in fluid responsiveness among intervention patients requiring mechanical ventilation vs those not requiring mechanical ventilation (32.1% vs 30.8%, $P = .94$). Among the intervention patients, no statistically significant difference was found between fluid responders and fluid

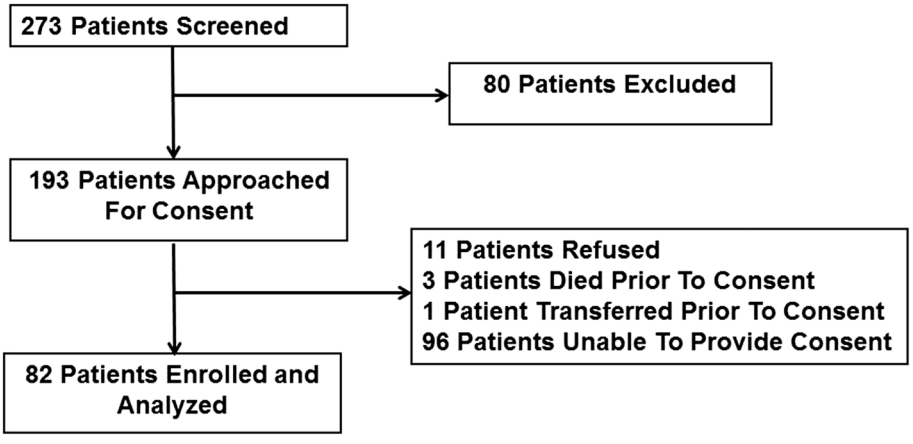

Figure 2 – *Patient flow diagram.*

TABLE 1] Patient Characteristics

Characteristic	Control Arm (n = 41)	Intervention Arm (n = 41)	*P* Value
Age, y	60 (50-68)	58 (45-65)	.35
Male sex	21 (51.2)	20 (48.8)	.83
BMI, kg/m^2	31.13 (25.98-37.41)	32.62 (24.37-37.85)	.93
Severity of illness score			
APACHE II score	26 (20.5-30)	25 (22-28.5)	.66
SOFA score	12 (11-15)	13 (11-15)	.54
Intubated	31 (75.6)	28 (68.3)	.46
ARDS	25 (61.0)	26 (63.4)	.82
Comorbidities			
COPD	7 (17.0)	5 (12.2)	.54
Hypertension	19 (46.3)	14 (34.1)	.26
Hyperlipidemia	10 (24.3)	10 (24.3)	1.0
Diabetes mellitus	10 (24.3)	12 (29.4)	.62
Systolic heart failure	5 (12.2)	4 (9.7)	.73
Heart failure with preserved ejection fraction	4 (9.7)	4 (9.7)	1.00
Chronic kidney disease	3 (7.3)	6 (14.6)	.29
Active malignancy	10 (24.3)	16 (39.0)	.16
End-stage liver disease	7 (17.0)	13 (31.7)	.12

Data are given as median (IQR) or No. (%). APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

nonresponders for cumulative fluids administered during the study period (10,891 mL [8,529-12,666 mL] vs 8,493 mL [5,059-11,125 mL], $P = .149$) and net fluid balance (452 mL [−2,370 to 5,201 mL] vs 2,844 mL [−3,283 mL to 9,383 mL], $P = .785$).

No statistically significant difference was found between the two groups in the median cumulative volume of study fluids administered by days 3 or 5 (Table 3). There was no statistically significant difference between the arms in the median volume of nonstudy fluids administered by days 3 or 5. Twenty patients had received blood products by day 3, and 24 patients had received blood products by day 5, but there was no difference between the arms in the median transfusion volume. There was no statistically significant difference between the two groups in the median net fluid balance by days 3 or 5. There was no statistically significant difference between the arms in secondary outcomes (Table 4).

Discussion

This pilot study suggests that TFM in patients with septic shock can be performed using protocol-guided assessments of fluid responsiveness. The results of this study could be used to help design a larger trial to verify the safety of using TFM in septic shock.

TABLE 2] Fluid Responsiveness Assessment and Treatment of Intervention Group (n = 41)

Day	Fluid Responsive	Goal-Directed IVF Administered[a]	Fluid Nonresponsive	Intervention[b]		
				CIVF	D	RRT
1 (n = 41)	13 (31.7)	13 (100)	28 (68.3)	28 (100)	7 (25.0)	12 (42.9)
2 (n = 41)	5 (12.2)	5 (100)	36 (87.8)	36 (100)	8 (22.2)	13 (36.1)
3 (n = 36)	2 (5.6)	2 (100)	34 (94.4)	34 (100)	12 (35.3)	14 (41.2)
4 (n = 35)	0 (0.0)	NA	35 (100)	35 (100)	8 (22.9)	14 (40.0)
5 (n = 31)	0 (0.0)	NA	31 (100)	31 (100)	8 (25.8)	13 (41.9)

Data presented as No. (%). CIVF = concentration of all IV fluid; D = diuretic therapy; IVF = IV fluid; NA = not applicable; RRT = renal replacement therapy.
[a]IVF boluses administered until fluid responsiveness resolved.
[b]Administered as part of fluid minimization strategy outlined in Figure 1.

TABLE 3] Primary Outcomes

Fluid	Control Arm		Intervention Arm		*P* Value
	No.	Volume	No.	Volume	
Study fluid, mL					
Day 3	38	4,110 (2,702 to 10,004)	36	4,417 (3,139 to 6,528)	.47
Day 5	31	8,690 (4,211 to 13,197)	31	6,244 (5,106 to 8,497)	.26
Nonstudy fluid, mL					
Day 3	38	1,854 (735 to 4,608)	36	1,664 (971 to 2,384)	.76
Day 5	31	2,660 (1,213 to 4,608)	31	2,920 (1,418 to 3,628)	.99
Net fluid output, mL					
Day 3	38	4,770 (2,021 to 6,479)	36	3,744 (2,354 to 6,163)	.77
Day 5	31	6,924 (3,351 to 11,968)	31	7,728 (3,146 to 1,0360)	.76
Net fluid balance, mL					
Day 3	38	3,124 (767 to 10,103)	36	1,952 (48 to 5,003)	.20
Day 5	31	3,616 (−1,513 to 9,746)	31	2,641 (−1,837 to 5,075)	.40

Data are presented as median (IQR). See Table 1 legend for expansion of abbreviation.

More than 15 years ago, Mitchell et al[5] performed a randomized, prospective trial at Barnes-Jewish Hospital to evaluate whether fluid management that emphasized diuresis and fluid restriction in patients with pulmonary edema could affect the development or resolution of extravascular lung water (EVLW), time on mechanical ventilation, and mortality in critically ill patients. Patients were randomized to an EVLW management group using a protocol based on bedside indicator-dilution measurements of EVLW or to usual care for that time. The study groups were managed differently as evidenced by a cumulative median input-output of 1,600 mL in the standard therapy group vs 754 mL in the EVLW group ($P = .001$). EVLW decreased significantly, and the number of ventilator-days and ICU days was significantly smaller only in patients from the EVLW management group. No clinically significant adverse effects occurred as a result of following the EVLW group algorithm. These findings were supported by the ARDS Clinical Trials Network study of conservative fluid management in ARDS, which found no significant difference in 60-day mortality.[3] However, conservative fluid management was associated with improved lung function and a shorter duration of mechanical ventilation and intensive care.

A positive fluid balance has also been associated with increased mortality rates in patients with septic shock. Boyd et al[9] performed a retrospective analysis of data collected during the Vasopressin in Septic Shock Trial (VASST), demonstrating that a more positive fluid balance at 12 h and at 4 days was independently associated with an increased risk of mortality. A retrospective analysis performed at our institute demonstrated similar results, with nonsurvivors having a significantly larger positive net fluid balance within 24 h of septic shock onset as compared with survivors (median, 4,374 mL [1,637-7,260 mL] vs 2,959 mL [1,639.5-4,769.5 mL]).[8] Being in the greatest quartile of positive net fluid

TABLE 4] Secondary Outcomes

Outcome	Control Arm (n = 41)	Intervention Arm (n = 41)	*P* Value
Renal replacement therapy	16 (39.0)	17 (41.5)	.82
Maximal vasopressor dose, μg/min	13 (7-25)	18 (9-35)	.15
Vasopressor days	4 (2-6)	4 (2-8)	.84
Vasopressor-free days	5 (0-16)	5.5 (0-10)	.84
Ventilator days	5 (3-9)	8 (3.25-15.25)	.30
Ventilator-free days	5.5 (0-16.75)	5.5 (0-12.25)	.05
In-hospital mortality	20 (48.8)	23 (56.1)	.51

Data are expressed as median (IQR) or No. (%). See Table 1 legend for expansion of abbreviation.

balance 8 days after shock was independently predictive of hospital mortality (OR, 1.66).

Our pilot study has several important limitations. First, the study was performed at a single center, and the results may not be generalizable. Second, there may be an undetected crossover effect because baseline hemodynamic characteristics were made available to the primary team in all patients in both arms. Although no data interpretation or therapeutic recommendations were provided for patients in the usual care arm, it is still possible that the availability of the baseline data changed the primary teams' behavior. Similarly, it is possible that a Hawthorne effect was present in our investigation. It is very conceivable that the physicians caring for the patients in the control group developed a tendency to either increase their monitoring efforts or attempt to improve fluid management for their patients enrolled in this trial, knowing that patient outcomes were being assessed. Finally, a potential bias may have existed in our study in the intervention group because the passive leg raise maneuver was not used in all patients to assess fluid responsiveness in lieu of the primary team deciding to administer IVF.

We failed to demonstrate significant differences between the two treatment groups in this pilot investigation. This was probably because of the design of this study, in which fluid therapies were not changed directly by the research team, but rather only therapeutic recommendations were made to the primary team for patients in the intervention arm, which may have resulted in less aggressive fluid restriction than may have otherwise occurred. Our experience suggests that future studies of TFM should more clearly separate the study groups being evaluated in terms of therapeutic interventions. One way of accomplishing this would be to mandate the use of diuretics with targeted net fluid balance goals in the intervention arm for patients not requiring renal replacement therapy. Fewer than one-half of the patients in the TFM therapy group who were eligible to receive diuretics actually got such therapy. Similarly, directed targets for fluid removal when renal replacement therapy is required could increase net fluid removal to achieve fluid balance differences between the study groups. Using a uniform practice of performing passive leg raise maneuvers to assess fluid responsiveness in the intervention arm should also be considered for any future trial of TFM. This approach could further differentiate the total amount of IVF administered, and thus the net fluid balance, between the treatment groups.

Conclusions

In conclusion, this pilot study suggests that TFM therapy following initial goal-directed therapy in patients with septic shock can be performed using protocol-guided assessments of fluid responsiveness. These pilot data should not be used to recommend the routine use of a TFM practice in septic shock; rather, these data should be used to help design a larger prospective trial examining the safety and efficacy of TFM in septic shock.

Acknowledgments

Author contributions: M. H. K. takes responsibility for the content of the manuscript and the data and analysis, including and especially any adverse effects. C. C. and M. H. K. contributed to the conception and design, acquisition of data, and analysis and interpretation of data; drafting of the submitted article and critical revision for important intellectual content; final approval of the version to be published; and accountability for all aspects of the work, including ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: M. H. K. is supported by the Barnes-Jewish Hospital Foundation. None declared (C. C.).

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