Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

John H. Boyd, MD, FRCP(C); Jason Forbes, MD; Taka-aki Nakada, MD, PhD; Keith R. Walley, MD, FRCP(C); James A. Russell, MD, FRCP(C)

Objective: **To determine whether central venous pressure and fluid balance after resuscitation for septic shock are associated with mortality.**

Design: **We conducted a retrospective review of the use of intravenous fluids during the first 4 days of care.**

Setting: **Multicenter randomized controlled trial.**

Patients: **The Vasopressin in Septic Shock Trial (VASST) study enrolled 778 patients who had septic shock and who were receiving a minimum of 5 μg of norepinephrine per minute.**

Interventions: **None.**

Measurements and Main Results: **Based on net fluid balance, we determined whether one's fluid balance quartile was correlated with 28-day mortality. We also analyzed whether fluid balance was predictive of central venous pressure and furthermore whether a guideline-recommended central venous pressure of 8–12 mm Hg yielded a mortality advantage. At enrollment, which occurred on average 12 hrs after presentation, the average fluid balance was +4.2 L. By day 4, the cumulative average fluid balance was +11 L. After correcting for age and Acute Physiology and Chronic Health Evaluation II score, a more positive fluid balance at both at 12 hrs and day 4 correlated significantly with increased mortality. Central venous pressure was correlated with fluid balance at 12 hrs, whereas on days 1–4, there was no significant correlation. At 12 hrs, patients with central venous pressure <8 mm Hg had the lowest mortality rate followed by those with central venous pressure 8–12 mm Hg. The highest mortality rate was observed in those with central venous pressure >12 mm Hg. Contrary to the overall effect, patients whose central venous pressure was <8 mm Hg had improved survival with a more positive fluid balance.**

Conclusions: **A more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Central venous pressure may be used to gauge fluid balance ≤12 hrs into septic shock but becomes an unreliable marker of fluid balance thereafter. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 hrs. (Crit Care Med 2011; 39:259–265)**

KEY WORDS: sepsis; septic shock; fluid resuscitation

Septic shock is an extremely complex disorder whose deranged physiology results from the interplay among the initial infection, the host response, and subsequent medical interventions. Despite exciting new discoveries characterizing molecular events during septic shock (1–3), some basic treatments remain understudied. Intravenous fluids, along with antibiotics, source control, vasopressors, inotropic agents, and mechanical ventilation, are a key component in the early management of septic shock (4). Surprisingly, despite current mortality rates of approximately 40% (5–8), dosing intravenous fluid during resuscitation of septic shock remains largely empirical. Too little fluid may result in tissue hypoperfusion and worsen organ dysfunction (4); however, overprescription of fluid appears to carry its own risks. In a recent European survey of critically ill patients with sepsis, a positive fluid balance was associated with increased mortality (9), whereas positive fluid balance increased time spent on mechanical ventilation and resulted in a trend toward increased mortality in a large randomized study of patients with acute lung injury (10). The 2008 Surviving Sepsis guidelines suggest the infusion of intravenous fluids until achieving a central venous pressure of 8–12 mm Hg and raise this target to 12–15 mm Hg in the presence of impaired ventricular filling/mechanical ventilation (4) However, there are no recommendations as to when it is appropriate discontinue or reduce the rate of administration of intravenous fluids.

Given the uncertainty surrounding fluid therapy for patients with septic shock, we conducted a retrospective review of 778 patients from the VAsopressin in Septic Shock Trial (VASST). All patients had septic shock and were receiving a minimum of 5 μg norepinephrine per minute. Correcting for age and severity of illness, we analyzed whether a positive fluid balance in the first 12 hrs of resuscitation and during the next 4 days was associated with an increase in 28-day mortality. Most clinicians assign some weight to a patient's central venous pressure when deciding whether to administer fluids; therefore, we went on to deter-

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From the University of British Columbia Critical Care Research Laboratories, Heart + Lung Institute, St Paul's Hospital, Vancouver, British Columbia, Canada.

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For information regarding this article, E-mail: John.Boyd@hli.ubc.ca

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mine whether central venous pressure was correlated with fluid balance at 12 hrs and during the subsequent 4 days. After correcting for age and severity of illness, we stratified patients into central venous pressure groups. Using the Surviving Sepsis guidelines, we grouped patients into those who fell into the recommended range (central venous pressure 8–12 mm Hg), those with a central venous pressure <8 mm Hg, and those with a central venous pressure >12 mm Hg and analyzed whether those with a central venous pressure of 8–12 mm Hg had a survival advantage.

METHODS

Subjects. Institutional Review Board approval was obtained for the VASST study from the Institutional Review Boards, and written informed consent obtained from all subjects. The VASST study enrolled 778 patients who had septic shock and who were receiving a minimum of 5 μg norepinephrine per minute. The VASST patient database included daily fluid intake and urine output for the first 4 days of treatment, central venous pressure, and Acute Physiology and Chronic Health Evaluation (APACHE) II score.

Analysis. We conducted a retrospective review of the use of intravenous fluids during the first 4 days of care and correlated fluid balance (defined as all oral and intravenous intake recorded on nursing flow sheets minus urine output and/or dialysis net output) with daily central venous pressure and 28-day mortality.

Statistical Analysis. We hypothesized that the benefit or harm from fluid administration would be nonlinear; in other words, both too little and too much fluid would be harmful. Therefore, for subsequent analyses, we divided patients into fluid balance quartiles. Survival analysis was performed using Cox stratified survival analysis and regression analysis with the Breslow method of ties. Stratification was for fluid balance quartiles or central venous pressure groups depending on the analysis. Age and severity of illness are the most prominent confounding variables with respect to risk of mortality in critically ill patients. To account for this, we used Cox regression analysis stratified according to fluid balance quartiles or central venous pressure groups and included age, APACHE II score, and dose of norepinephrine as covariates. Hazard ratios were calculated relative to 1) quartile 4 fluid balance; or 2) the central venous pressure >12 mm Hg groups using Cox proportional hazards, again controlling for age, APACHE II score, and dose of norepinephrine. Hazard ratios are presented with their 95% confidence intervals. Differences in fluid balance between survivors and nonsurvivors was analyzed with the Mann-Whitney rank sum test.

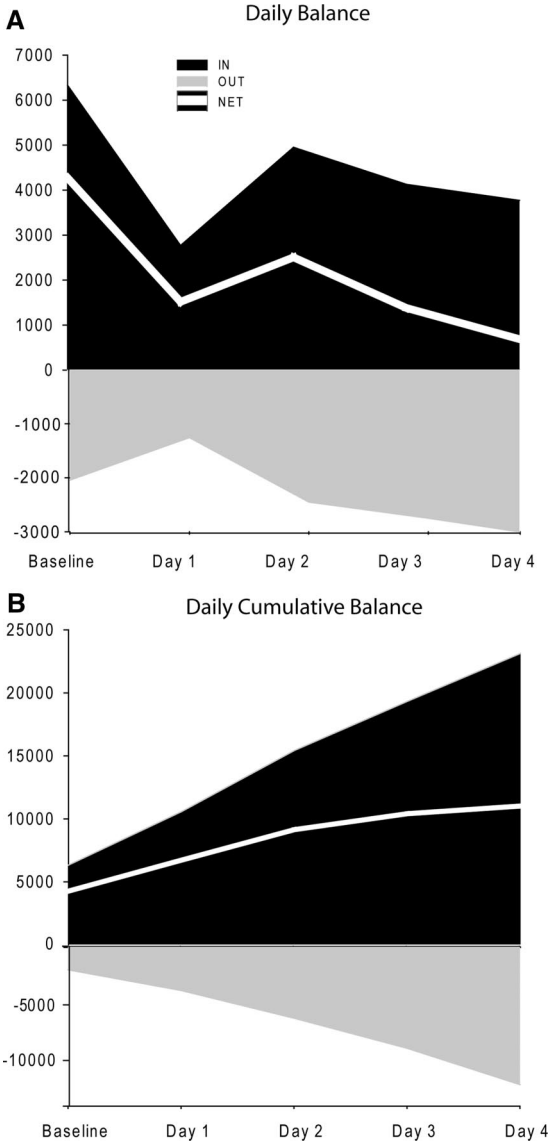

Figure 1. *A*, Daily fluid intake, urine output and fluid balance at 12 hrs and days 1–4. *B*, Cumulative daily fluid intake, urine output and fluid balance at 12 hrs and days 1–4.

RESULTS

The Rate of Fluid Accumulation Was Greatest During the Initial Resuscitation But Remained Positive Throughout the First 4 Days. Increases in positive fluid balance were mainly influenced by dosing of intravenous fluids rather than decreases in urine output. At a mean time of 12 hrs (after enrollment in the study), the average positive fluid balance was 4.2 ± 3.8 L (Fig. 1*A–B*). The dose of intravenous fluids was 6.3 ± 3.5 L, whereas urine output averaged 2.0 ± 2.3 L. Average fluid balances on days 1, 2, 3, and 4 were 1.5 ± 1.8 L, 2.5 ± 2.8 L, 1.4 ± 2.3 L, and .69 ± 2.1 L, respectively (Fig. 1*A*). Cumulative fluid balance by day 4 averaged 11 ± 8.9 L (Fig. 1*B*). Twelve-hr and day 4 fluid balances (quartiles expressed as median and 25–75% ranges) are shown in Table 1. As shown in Table 1, although the increase in positive fluid balance was driven both by increased prescription of fluid and reduced urine output, intake appeared to dominate with an interquartile difference quartile 4 to quartile 1 at 12 hrs of 7200 mL compared with a difference of only −1000 mL in urine output. Cumulative fluid balance at 4 days showed a similar pattern with a fluid intake interquartile difference from quartile 4 to quartile 1 of 14,500 mL compared with a −6250-mL difference in urine output.

Fluid Balance Predicts Mortality Both At 12 Hrs and at Day 4. Adjusted survival curves are shown in Figure 2. Both at 12 hrs and day 4, one's fluid balance quartile

Table 1. Fluid intake, urine output, and net fluid balance at 12 hrs and cumulative day 4 balance

	Quartile 1 (Dry)	Quartile 2	Quartile 3	Quartile 4 (Wet)
12 hrs				
Intake, mL	2900 (2050–3900)	4520 (3700–5450)	6110 (5330–7360)	10,100 (8430–12,100)
Output, mL	2200 (1100–3920)	1590 (960–2560)	1180 (600–2070)	1260 (600–2400)
Balance, mL	710 (−132–1480)	2880 (2510–3300)	4900 (4290–5530)	8150 (7110–10,100)
Day 4				
Intake, mL	16,100 (12,800–19700)	18,500 (15,700–22,500)	22,800 (19,700–26,700)	30,600 (26,200–36,000)
Output, mL	14,600 (11,500–20100)	11,000 (8210–14,500)	9960 (6940–12,900)	8350 (5100–12,300)
Balance, mL	1560 (−723–3210)	8120 (6210–9090)	13,000 (11,800–14,700)	20,500 (17,700–24,500)

Volumes are expressed as median (25–75%).

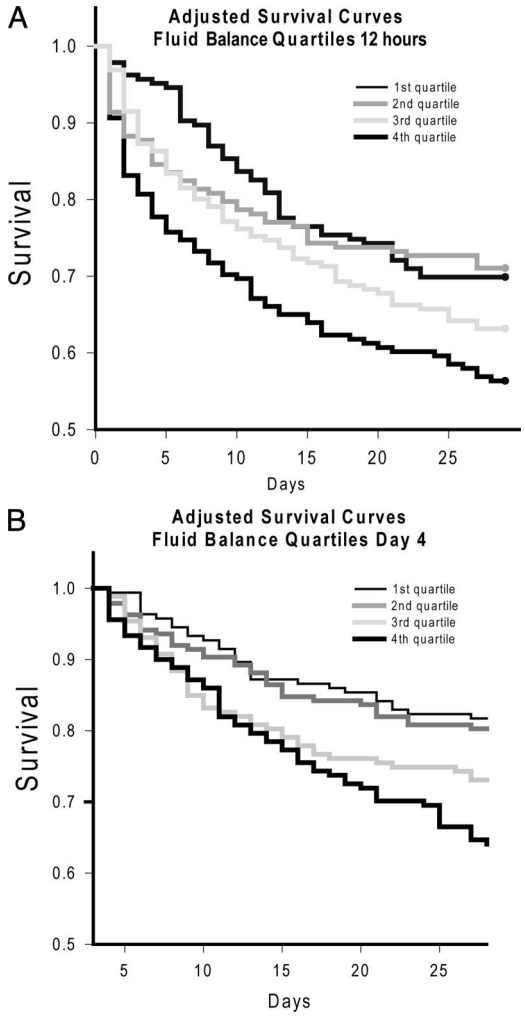

Figure 2. *A*, Cox survival curves, adjusted for age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and severity of shock (dose of norepinephrine), are shown for fluid balance quartiles at 12 hrs. Quartiles 3 and 4 have significant increases in mortality compared with both quartiles 1 and 2. *B*, Cox survival curves, adjusted for age, APACHE II score, and dose of norepinephrine, are shown for cumulative fluid balance quartiles at day 4. Quartiles 3 and 4 have significant increases in mortality compared with both quartiles 1 and 2.

predicted mortality. At 12 hrs, compared with quartile 4, the risk of mortality (adjusted hazard ratio) in quartiles 1–2 were significantly reduced (Table 2). Quartile 3 showed a nonsignificant trend to decreased mortality as well with an adjusted hazard ratio of 0.762 (0.562–1.033). Cumulative fluid balance on day 4 also correlated with mortality with quartile 1 and 2 having survival advantages compared with quartile 4 (Table 2). Again quartile 3 demonstrated a nonsignificant trend toward decreased mortality.

Fluid Balance Correlates Modestly With Central Venous Pressure and Dose of Norepinephrine at 12 Hrs, Whereas There Is No Significant Association by Day 4. We assessed whether the incident fluid balance can predict central venous pressure at 12 hrs and whether the preceding 24-hr fluid balance can predict central venous pressure thereafter. Using linear regression analysis, we found that fluid balance only correlated with central venous pressure in a statistically significant manner at 12 hrs. This correlation was very modest with an R correlation of 0.2 and $p < .001$. Fluid balance also correlates modestly with dose of norepinephrine at 12 hrs ($r = .2$ and $p < .001$). Even this modest correlation between central venous pressure and fluid balance disappeared during the next 24 hrs with an R correlation of $< .02$ on each subsequent day until day 4. Similarly, after enrollment, there was no significant correlation between dose of norepinephrine and fluid balance. Figure 3 graphically represents the relationship between incident fluid balance and central venous pressure or dose of norepinephrine at 12 hrs as well as day 4.

A Central Venous Pressure of <8 mm Hg at 12 Hrs Is Associated With Improved Survival, Whereas Central Venous Pressure Does Not Correlate With Mortality on Subsequent Days. Given the 2008 Surviving Sepsis Guideline recommendation to target a central venous pressure of 8–12 mm Hg to ensure adequate intravascular volume, we assessed whether achieving this target was associated with improved survival. We grouped patients into those with a 12 hrs central venous pressure <8 mm Hg, those with a central venous pressure 8–12 mm Hg, and those in whom central venous pressure was >12 mm Hg. We used Cox regression analysis stratified according to central venous pressure group and included age and APACHE II score as co-

variates. Adjusted survival curves are shown in Figure 4. As shown in Figure 4 and Table 3, at 12 hrs, those in the central venous pressure <8 mm Hg group had a higher survival compared with those with central venous pressure >12 mm Hg. Patients whose central venous pressure was 8–12 mm Hg had a higher mortality rate than those with central venous pressure <8 mm Hg but still had a survival advantage over those with central venous pressure >12 mm Hg. During days 1–4, there were no significant differences in survival according to central venous pressure group. Using day 4 as representative of post-12-hr events, Figure 4*B* and Table 3 show the overlapping survival curves and nonsignificant hazard ratios from the three central venous pressure groups.

Table 2. Hazard ratio for death according to fluid balance quartiles

Fluid Balance Group	Adjusted Hazard Ratio versus Quartile 4
12 hrs	
Quartile 1	0.569 (0.405–0.799)
Quartile 2	0.581 (0.414–0.816)
Quartile 3	0.762 (0.562–1.033)
Day 4	
Quartile 1	0.466 (0.299–0.724)
Quartile 2	0.512 (0.339–0.775)
Quartile 3	0.739 (0.503–1.087)

Hazard ratios are shown with their 95% confidence intervals.

At 12 Hrs, a Less Positive Fluid Balance Was Associated With Lower Mortality Overall; However, This Reversed in Those Whose Central Venous Pressure Was <8 mm Hg. At 12 hrs, we found that both central venous pressure and fluid balance were correlated with mortality. We reasoned that if central venous pressure and/or fluid balance influenced mortality rather than impending mortality being determinate, there could be independent interactions among all three variables. Overall, as shown in Table 4, survivors had a lower positive fluid balance than nonsurvivors (3444 mL vs. 4429 mL). Interestingly, in patients whose central venous pressure was <8 mm Hg, survivors trended toward a more positive fluid balance (3015 mL) than nonsurvivors (2281 mL). In patients whose central venous pressure was 8–12 mm Hg, the opposite was true with survivors trending to a less positive fluid balance (2727 mL) compared with nonsurvivors (3112 mL). Finally, in patients whose central venous pressure was >12 mm Hg, survivors had a large and statis-

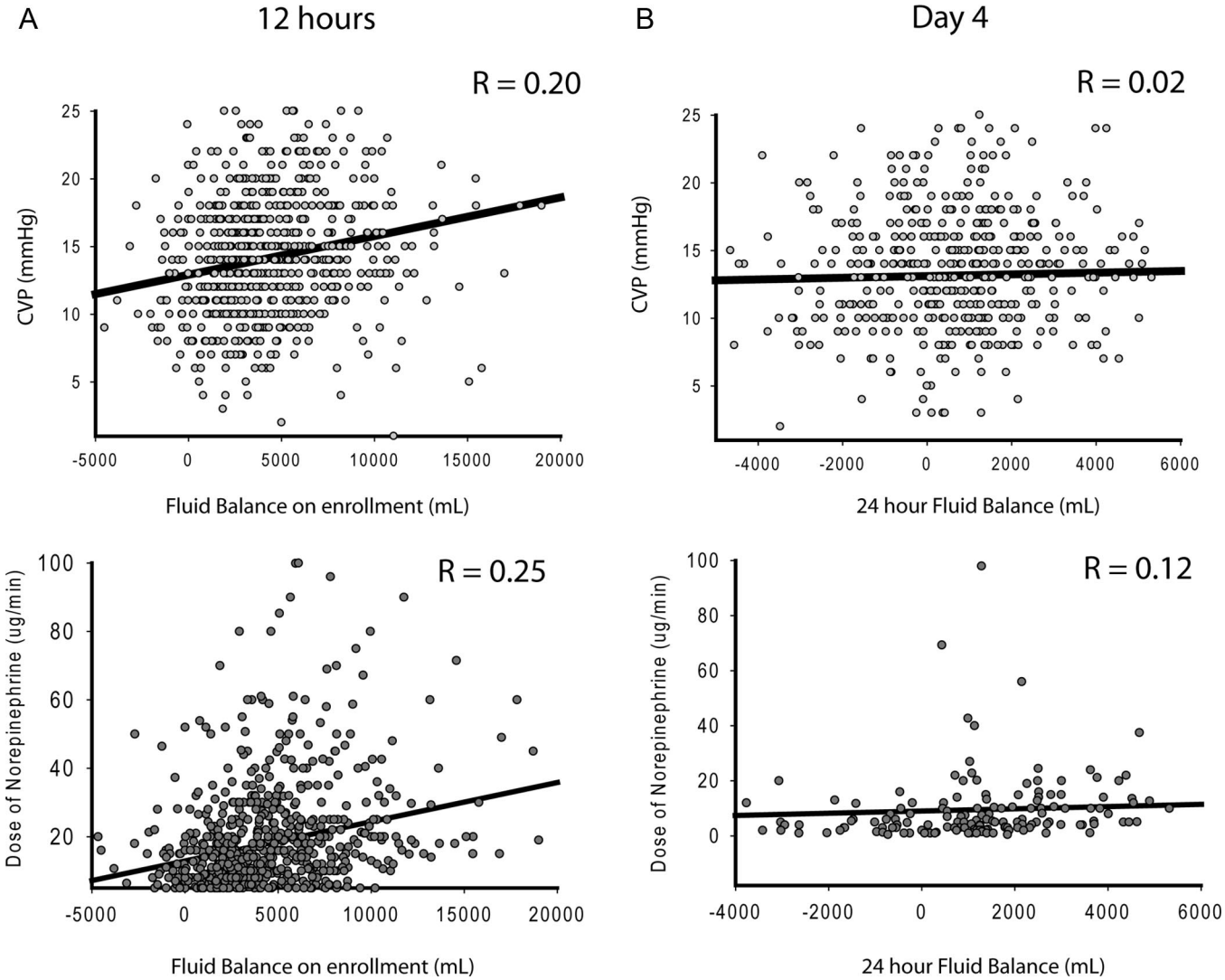

Figure 3. *A*, Fluid balance on study enrolment (12 hrs) significantly correlates with central venous pressure and dose of norepinephrine, $p < .001$ in both cases. *B*, Day 4 fluid balance during the preceding 24 hrs does not correlate with central venous pressure nor with the dose of norepinephrine.

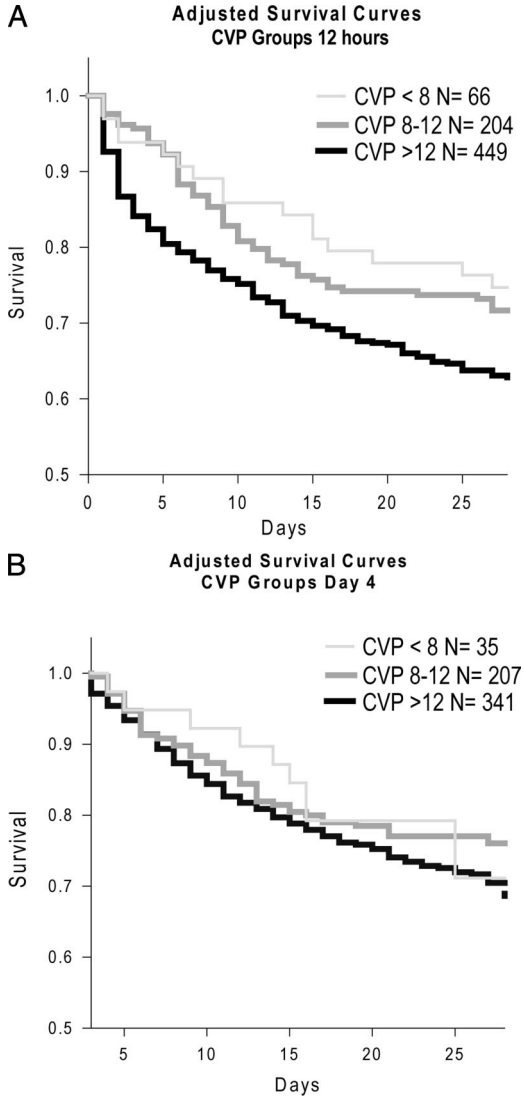

Figure 4. *A*, Cox survival curves, adjusted for age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and severity of shock (dose of norepinephrine), are shown for central venous pressure (*CVP*) groups at 12 hrs. Patients with a CVP of <8 mm Hg at 12 hrs have the lowest mortality followed by those with CVP of 8–12 mm Hg and patients with a CVP >12 mm Hg had the highest mortality. B, Cox survival curves, adjusted for age, APACHE II score, and dose of norepinephrine, are shown for CVP groups on day 4. There were no significant differences in mortality among groups.

Table 3. Hazard ratio for death according to CVP group

CVP Group	Adjusted Hazard Ratio versus CVP >12 mm Hg
12 hrs	
CVP <8 mm Hg	0.606 (0.363–0.913)
CVP 8–12 mm Hg	0.762 (0.562–0.943)
Day 4	
CVP <8 mm Hg	0.903 (0.484–1.686)
CVP 8–12 mm Hg	0.764 (0.542–1.078)

CVP, central venous pressure.

Hazard ratios are shown with their 95% confidence intervals.

tically significant decrease in positive fluid balance compared with nonsurvivors (3975 mL vs. 5237 mL).

DISCUSSION

Whether the administration of intravenous fluid is likely to improve organ perfusion and impact survival in septic shock is a question facing the caregiver nearly continuously throughout the resuscitation period. Unfortunately, there are no randomized controlled studies that address the dose of intravenous fluid for patients with septic shock. The Surviving Sepsis guidelines suggest targeting fluid therapy to a central venous pressure of 8–12 mm Hg to ensure adequate intravascular volume (4). This is based largely on the landmark 2001 study "Early goal-directed therapy in the treatment of severe sepsis and septic shock" (EGDT) (11), in which the first branch of the treatment algorithm is the administration of intravenous fluid to achieve a central venous pressure between 8 and 12 mm Hg. Interestingly, it was not explicitly stated within the EGDT protocol how the clinician could identify when to stop volume infusion (11). This lack of a "cap" or cutoff for fluid administration continued into the Surviving Sepsis guidelines (4). How should a clinician faced with a patient in vasopressor-dependent shock titrate fluid therapy? The VASST study provides an excellent opportunity to study the usual prescribing practices for intravenous fluids in patients with septic shock, because neither before nor after enrollment was there a mandatory fluid administration protocol, leaving this to the discretion of the treating physician (7).

Perhaps as a result of the publication and subsequent rapid adoption by the intensive care unit community of EGDT as standard of care during enrollment into the VASST study, the average dose of intravenous fluids in these studies was similar. The 12-hr period including initial diagnosis and early resuscitation before enrollment into VASST (baseline) defined a period spent in the emergency department similar to the EGDT study period. At 12 hrs, VASST patients had received 6.3 L of fluid with a positive fluid balance of 4.2 L. There was significant interpatient variability as reflected in a SD in fluid balance of 3.8 L with the median quartile fluid balances ranging from +710 mL positive (quartile 1) to +8200 mL (quartile 4). In the Rivers study, subjects randomized to EGDT received an average of 5 L of intravenous fluid, whereas those in the standard care arm received 3.5 L in the 6-hr study window (11). Interestingly, although EGDT patients were prescribed 1.5 L more fluid in the 7-hr treatment period than standard care, during the full 72 hrs, both EGDT and standard care groups were eventually prescribed equal amounts of fluids (13.4 L). These investigators did not correlate fluid intake or fluid balance to subsequent mortality, but in a recent survey of 3147 patients admitted to 128 European intensive care units, a positive fluid balance did correlate with mortality (9). In the VASST study, we found that a more positive fluid balance at 12 hrs and a

Table 4. 12-hr fluid balance: Survivors vs. nonsurvivors within CVP groups

CVP Group	Net Fluid Balance		p
	Survivors	Nonsurvivors	
All Patients	3444 (1861–5984) mL	4429 (2537–6560) mL	<.001
CVP <8 mm Hg	3015 (1296–4987) mL	2281 (802–5711) mL	NS
CVP 8–12 mm Hg	2727 (1227–5491) mL	3112 (1559–4809) mL	NS
CVP >12 mm Hg	3975 (2387–6614) mL	5237 (3140–7773) mL	<.001

CVP, central venous pressure; NS, nonsignificant.
Volumes are expressed as median (25–75%).

more positive cumulative balance at day 4 significantly increased 28-day mortality. The large increases in the hazard of mortality with increasingly positive fluid balance quartiles appeared to be independent of severity of illness, a major potential confounder.

Of 719 patients with central venous pressures recorded at 12 hrs, only 204 (28%) had the recommended (4) central venous pressure of 8–12 mm Hg. The majority of patients, 449 of 719 (62%), had a central venous pressure >12 mm Hg, whereas only 9% had a central venous pressure <8 mm Hg. At 12 hrs, there was a significant correlation between central venous pressure and the preceding fluid balance. Many have argued that volume status of patients who have septic shock cannot be accurately gauged and monitored by central venous pressure because of changes of ventricular compliance, changes in thoracic and lung compliance, and frequent use of positive pressure ventilation in septic shock. Our findings suggest that even early in the course of septic shock, central venous pressure cannot stand alone as an indicator of volume status. Why might have the majority of clinicians continued fluid administration despite having achieved a central venous pressure of 8–12 mm Hg? The VASST study enrolled patients from July 2001 to August 2006. The first iteration of the Surviving Sepsis guidelines did not appear until 2004 (12); before that, the choice of target central venous pressure was largely empirical. It is also possible that a significant proportion of treating physicians believed their patient had decreased ventricular compliance and targeted a central venous pressure of 12–15 mm Hg, a strategy formally advocated in the 2008 Surviving Sepsis supplemental guideline (4). Furthermore, previous guidelines suggest infusing fluids with pulmonary edema as a defined limit (13). After confirming that 12-hr central venous pressure was modestly correlated to fluid balance, we addressed whether achieving a central venous pressure of 8–12 mm Hg resulted in a reduction in mortality compared with those with central venous pressures outside of this range. The Surviving Sepsis guidelines based their recommendation largely on the central venous pressure target from the EGDT study (4, 11). In that study, both EGDT and standard therapy groups met the target central venous pressure for most of the resuscitation period with a time-integrated mean central venous pressure of 11.7 mm Hg in the EGDT group and 10.5 in the standard arm (11). By 6 hrs, EGDT patients had mean central venous pressures of 13.8 mm Hg, whereas standard care was a mean of 11.8 mm Hg. Was the 16% absolute reduction in mortality with EGDT a result of achieving a central venous pressure of 13.8 rather than 11.8 mm Hg or might it be that other factors, including large differences in the use of inotropes and blood transfusion, drove the treatment effect (11)?

In VASST patients at 12 hrs, having a central venous pressure >12 mm Hg conferred the highest risk of mortality, whereas those with a central venous pressure of <8 mm Hg had a survival advantage over those with 8–12 mm Hg and those with central venous pressures >12 mm Hg. This relationship between higher central venous pressure and increased hazard of death was independent of the severity of illness as assessed by APACHE II score. However, in patients whose central venous pressure was <8 mm Hg, we found a more positive fluid balance among survivors compared with nonsurvivors, suggesting that there is a point at which too little fluid is indeed harmful. Pooling data from the fluid balance quartiles at 12 hrs (separation of the mortality curves occurs mainly between quartiles 2 and 3) and the analysis performed in Table 4, it appears that optimal survival occurs with a positive fluid balance of approximately 3 L at 12 hrs. When we examined analyzed patients with established septic shock (days 1–4), we found no correlation between central venous pressure and fluid balance. Thus, it seems that after the initial 12 hrs in septic shock, central venous pressure is not only unable to predict fluid responsiveness (an increase in cardiac output following fluid challenge) (14, 15), but is an unreliable marker of fluid balance.

Higher positive fluid balance and/or higher central venous pressure in the VASST study was associated with increased mortality. Our findings build on earlier work including the observational Sepsis Occurrence in Acutely Ill Patients study in which positive fluid balance was associated with increased mortality (9), two retrospective analyses in which negative fluid balance was associated with improved survival in septic shock (16, 17), and in patients with acute respiratory distress syndrome in whom a restrictive fluid strategy decreased length of mechanical ventilation, decreased intensive care unit length of stay, and a trend to a decrease in mortality (10). Very recent studies have also found late fluid accumulation in patients with lung injury to be associated with increased mortality and length of stay (17, 18). How might the infusion of copious intravenous fluids lead to organ dysfunction and death? Whether through increased capillary permeability or through pulmonary venous vasoconstriction, large-volume resuscitation of sepsis has been found to increase extravascular lung water (19, 20). The resultant decrease in lung compliance and increase in respiratory workload is a potent force against successful weaning from mechanical ventilation. In the kidney, often an important contributor to a positive fluid balance resulting from acute injury, a recent report in critically ill patients suggests that volume overload at the time of dialysis confers an odds ratio of 2 for mortality (21). Furthermore, they found that independent of the severity of renal failure, volume overload decreases the likelihood of subsequent renal recovery (21), implying causation with respect to worsening renal failure.

The major limitation to this study is its retrospective nature. As such, we are unable to determine whether central venous pressure and fluid balance are simply markers of severity of illness or whether they independently affect outcome. Although we adjusted for age, APACHE II score, and severity of shock, it

is possible that an unappreciated and undocumented confounder (such as mottled extremities) was both a predictor of mortality and drove increased fluid administration. Another limitation is that the type of intravenous fluid (ie, colloid, crystalloid, etc) was not documented. A prospective randomized study of liberal vs. restrictive fluid management of patients in septic shock is required to definitively prove whether positive fluid balance is a "biomarker" for severity of illness or whether the administration of excess fluids causes mortality.

CONCLUSIONS

A more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Central venous pressure may be useful along with other measures to gauge adequacy of fluid resuscitation ≤12 hrs into septic shock but becomes an unreliable marker of fluid balance thereafter. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 hrs.

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