Interaction Between Fluids and Vasoactive Agents on Mortality in Septic Shock: A Multicenter, Observational Study*

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Objective: Fluids and vasoactive agents are both used to treat septic shock, but little is known about how they interact or the optimal way to administer them. We sought to determine how hospital mortality was influenced by combined use of these two treatments.

Design: Retrospective evaluation using multivariable logistic regression to evaluate the association between hospital mortality and categorical variables representing initiation of vasoactive agents and volumes of IV fluids given 0–1, 1–6, and 6–24 hours after onset, including interactions and adjusting for potential confounders.

Setting: ICUs of 24 hospitals in 3 countries.

Patients: Two thousand eight hundred forty-nine patients who survived more than 24 hours after after onset of septic shock, admitted between 1989 and 2007.

Interventions: None.

Measurements and Main Results: Fluids and vasoactive agents had strong, interacting associations with mortality ($p < 0.0001$). Mortality was lowest when vasoactive agents were begun 1–6 hours after onset, with more than 1 L of fluids in the initial hour after shock onset, more than 2.4 L from hours 1–6, and 1.6–3.5 L from 6 to 24 hours. The lowest mortality rates were associated with starting vasoactive agents 1–6 hours after onset.

Conclusions: The focus during the first hour of resuscitation for septic shock should be aggressive fluid administration, only thereafter starting vasoactive agents, while continuing aggressive fluid administration. Starting vasoactive agents in the initial hour may be detrimental, and not all of that association is due to less fluids being given with such early initiation of vasoactive agents. (*Crit Care Med* 2014; 42:2158–2168)

Key Words: resuscitation; septic shock; statistical models; vasoactive agonists

***See also p. 2294.**

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Development of the existing database used for this study was supported in the past by unrestricted grants from Lilly, Wyeth, Pfizer, Merck, AstraZeneca, Astellas, Manitoba Health Research Council, Manitoba Health Sciences Foundation, and the Deacon Foundation.

Dr. Kumar's institution received grant support from Astellas, Lilly, Pfizer, Merk, Bayer, GSK, and Roche (unrestricted grants). Dr. Marshall served as board member for Asahi Kasei Pharma America (Data Monitoring Committee Member, ART-123). Dr. Parrillo served as board member for Artisan, Sangart, and Cytosorbents. His institution received grant support from the Salem Foundation. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000000520

Septic shock is the reason for approximately 10% of ICU admissions and has mortality close to 50% (1, 2). In addition to antimicrobials and source control, use of IV fluids and vasoactive agents to correct hypotension and hypoperfusion are mainstays of treatment (3, 4).

Many published studies on resuscitation in septic shock have addressed the timing, volume, and composition of administered fluids. These studies have compared early versus late fluids (5), high versus low volumes (6–10), and resuscitation protocols versus no protocol (4, 10). Some have shown an association between fluid resuscitation and mortality, and others have not.

Studies comparing the effect of crystalloid versus colloid solutions on mortality have also had mixed results (11, 12).

Fewer studies have addressed the use of vasoactive agents in septic shock. Studies comparing different agents have not clarified the optimal agents, and none have addressed the optimal timing (13–15). A retrospective study suggesting that more norepinephrine might be harmful was likely confounded by indication bias (16). As a consequence, this element of care is mainly guided by expert opinion (3, 4, 17, 18).

Prominent among possible reasons for inconsistent findings in the existing literature assessing fluids or vasoactive agents is the fact that these two components of resuscitation are used simultaneously for the same indications of hypotension and hypoperfusion. The goal of this study of a cohort of ICU patients with septic shock was to clarify the association of hospital mortality with the timing, volume, and composition of IV fluids and with the timing of initiating vasoactive agents, allowing for interactions between the two modalities. Our a priori hypothesis was that there would be relevant interactions between these two treatments.

METHODS

We performed a retrospective review of medical records from 1989 to 2007 of consecutive adults (≥ 18 yr old) with septic shock in the ICUs of 28 hospitals in Canada, the United States, and Saudi Arabia. Not all institutions contributed data for all years of data collection. This dataset has been used for prior publications, in which details of data collection have been described (19–22). Data were collected by trained research personnel using a standardized and piloted data extraction template. All data collectors had at least 5% of their data extractions reviewed by the local principal investigator to ensure accuracy.

Potential cases of septic shock were initially identified using local ICU registries/databases and *International Classification of Diseases Revision 9 or 10* coding strategies applied to administrative databases. Each potential case was manually screened to determine if the case met specific criteria for septic shock, as described by the 1991 Society of Critical Care Medicine/American College of Chest Physicians Consensus Statement on Sepsis Definitions (23). The first measurement of hypotension that remained persistent was considered to be the onset of septic shock ("time zero").

Inclusion criteria for analysis in the present study included the following: 1) septic shock (23), 2) survival for at least 24 hours after the onset of hypotension to exclude survival bias (24), 3) administration of appropriate antimicrobials before or within 24 hours after the onset of hypotension (antimicrobials were considered appropriate if they demonstrated in vitro activity for isolated pathogens, or in the case of culture-negative septic shock, antimicrobial therapy matched accepted national guidelines) (21), 4) IV infusion of at least one vasoconstrictor drug within 24 hours after the onset of hypotension (including norepinephrine, phenylephrine, epinephrine, dopamine, or vasopressin, at any dosages), and 5) administration within 24 hours after onset of hypotension of greater than 0 but less than or equal to 20 L of IV fluids. Some institutions did not collect complete fluid data; records were excluded if data elements were missing.

Fluids were crystalloids or colloids, with the latter including albumin products and synthetic starches, regardless of concentration. Crystalloid volumes were normalized by tonicity, with isotonic solutions being the reference, for example, the volume of 0.45% saline was divided by two and added to the volumes of 0.9% saline and lactated Ringer's solution. The total volumes of all colloids (albumin and synthetic) were summed as administered, with the exception that the volume of 25% albumin was multiplied by five.

To assess how IV fluids and vasoactive agents were associated with hospital mortality, we used multivariable logistic regression. We accounted for the clustered nature of the data by use of Generalized Estimating Equations, using an exchangeable correlation structure (25), and robust (Huber-White) SEs. Statistical analysis was done with Stata 11 (College Station, TX). p values less than 0.05 were considered statistically significant.

Adjustment in this model was made for the following covariates: year in which the shock occurred, age, sex, chronic comorbid conditions, pre-ICU location, admission type, anatomic site of infection, severity of acute illness, and timing of administration of appropriate antibiotics. For year of shock, we assessed a linear trend. Our original dataset included 27 comorbidities. Based on their frequencies and known problems with internal validity, some of these were eliminated and others combined, leaving nine comorbid conditions: diabetes, immune suppression unrelated to malignancy, substance abuse, chronic renal failure, chronic obstructive pulmonary disease (COPD), metastatic cancer, liver dysfunction, hematologic malignancy, and organic brain disorders. Pre-ICU location was dichotomized as emergency department versus elsewhere. Admission type was categorized as emergency surgery, elective surgery, or nonsurgical. We included three measures of severity of illness, recorded as the most abnormal value within the initial 24 hours after onset of septic shock of: Acute Physiology and Chronic Health Evaluation (APACHE) II score (1), serum lactate (26), and the number of organ failures (23). Time to appropriate antibiotics was measured in hours from hypotension onset, with negative values assigned if given before onset. Age, APACHE II score, and serum lactate were transformed into four-knot restricted cubic splines; these piecewise polynomial expansions enable identification of nonlinear relationships of the native continuous variables with the outcome (27).

The primary variables of interest in the logistic regression were IV fluids given during the initial 24 hours of resuscitation and timing of initiating vasoactive drugs. To facilitate interpretation of possible interactions between fluids and vasoactive agents, we used categorized versions of these variables.

This database separated the initial 24 hours into three periods, timed from onset of hypotension: 0.00–0.99, 1.00–5.99, and 6.00–24.00 hours; for simplicity, we refer to these as 0–1, 1–6, and 6–24 hours. For each period, we created two fluid variables. The first variable, total equivalent volume (TEV), was calculated as crystalloid volume plus twice colloid volume; this ratio derives from comparative measurement of

intravascular-extravascular equilibration (10). For each time period, the three TEV variables were divided into low, intermediate, and high terciles (0–1 hr [TEV0–1]: 0–0.50, 0.51–1.00, and 1.01–9 L; 1–6 hr [TEV1–6]: 0–1.00, 1.01–2.40, and 2.41–13.6 L; 6–24 hr [TEV6–24]: 0–1.62, 1.63–3.50, and 3.51–16.8 L). The second fluid variable for each time interval was binary and indicated whether any colloids were given in that period. Data about transfusions of blood products, including plasma, were not available and therefore were not included in our analysis.

For alignment with the fluid variables, we used a single categorical variable indicating whether vasoactive therapy was begun 0–1, 1–6, or 6–24 hours after hypotension onset. The regression model of hospital mortality included all four-way interactions between this variable and the three categorized TEV variables. This resulted in a separate regression coefficient and estimate of hospital mortality for each of the 81 combinations of these four variables. These results represent the most relevant expression of our findings. For them to be generalizable beyond our specific patient cohort only requires that the relationship between these variables and mortality be representative of septic shock in general.

Because the TEV and vasoactive variables demonstrated complex interactions, we sought to provide a simpler expression of the results, by estimating the independent effects of a given variable on outcome. For this purpose, we used the *margins* command of Stata to calculate predicted hospital mortality of the entire cohort with different values of the variable of interest. It is important to appreciate the limitation of such information. Specifically, this analysis produced mortality rates (and *p* values to compare them) that would be predicted to occur if all patients in our cohort had the indicated value of the isolated variable, while keeping all other variables unchanged. For these findings to be generalizable requires, in addition to the requirement stated in the preceding paragraph, the additional and stronger requirement that the distribution of all other variables in our sample be the same as in the larger population of patients with septic shock. Indeed, in light of the strong interactions found in the full model, no rigorous and generalizable statements can be made about the isolated effect of changing one of the interacting variables.

We further explored the association between use of fluids and vasoactive agents by creating a linear regression model of TEV infused 0–6 hours after onset of hypotension, among patients whose vasoactive drugs were begun within that interval. In this model, the independent variable of interest was the timing of initiating vasoactive agents, represented as four-knot restricted cubic splines; it included the same additional covariates as above and likewise accounted for clustering within ICUs using Generalized Estimating Equations.

The Health Ethics Board of the University of Manitoba and each individual participating center approved this study, with a waiver of informed consent.

RESULTS

The database included 8,673 patients with septic shock cared for in 28 hospitals. Of the 4,716 patients who met inclusion criteria, 1,867 had missing data elements (usually fluid volumes). The remaining 2,849 individuals from 24 hospitals were used for analysis. Included patients (**Table 1**) had a mean age of 62 years, and 56% were men. Approximately half were admitted to ICU from emergency departments. The average (SD) APACHE II score was 26 (8), and hospital mortality was 47.4%. In multivariable regression analysis (**Table 2**), patient and illness characteristics that were significantly associated with hospital mortality included age, anatomic site of infection, severity of acute illness (as indicated by APACHE II score, serum lactate, and the number of organ failures), admission type, pre-ICU location, and five of the comorbid conditions (liver dysfunction, hematologic malignancy, metastatic cancer, COPD, and chronic renal failure). In addition, there was a small but significant decline in septic shock mortality over the 18-year study interval.

Volumes of crystalloids and colloids administered during each of the three time intervals after hypotension onset were highly variable (Table 1). The percentage of patients who received no crystalloids or colloids during the intervals 0–1, 1–6, and 6–24 hours after onset of hypotension were, respectively, 7.7%, 3.4%, and 3.5%. The percentages who received no colloids during those time intervals were 79.6%, 55.5%, and 41.6%, respectively. Vasoactive agents were begun a mean of 4.5 hours after onset of hypotension (median, 2.8 hr; interquartile range, 1.0–6.3), with three-quarters having such agents begun within 6 hours.

Multivariable regression analysis showed complex associations between hospital mortality and fluid timing and volume and vasoactive drug timing (**Tables** 2 and **3**; **Appendix Table A1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B13). The 81 combinations of fluid timing/volumes and vasoactive start times were associated with mortality estimates ranging from 24.7% to 71.1% ($p < 0.0001$). Lowest mortality was associated with the combination of treatments in which vasoactive agents were started 1–6 hours after hypotension onset, high volumes of fluid were given in the 0- to 1-hour and 1- to 6-hour intervals (median values, respectively, of 2.0 and 3.7 L), and a moderate volume (median value, 2.4 L) was given during the 6- to 24-hour period. Of these 81 mortality estimates, the features shared by the four combinations with the lowest mortality were that vasoactive agents were started 1–6 hours after hypotension onset, and high amounts of fluids were given within the first 6 hours. Mortality was not associated with the use versus nonuse of colloids in any of the three time intervals.

The simplified, but limited, analysis of the independent influences of the TEV and vasoactive drug timing variables shows that all the fluid volume and vasoactive timing variables were significant in isolation except for 0- to 1-hour fluid volume (**Table 4**). The largest independent influence in our cohort was the TEV of fluids administered during the 1- to 6-hour period (Table 3). Based on the model, giving every individual in our cohort low volume during that interval (median received was 0.5 L) would have been associated with a significantly higher mortality than if they all had received intermediate volume (median, 1.7 L; mortality

TABLE 1. Characteristics, Interventions, and Outcomes of 2,849 Patients With Septic Shock

Variable	Value	Range
Characteristic		
Age (yr)	61.8 ± 16.1	16, 102
Male sex, *n* (%)	1,585 (55.6)	
Acute Physiology and Chronic Health Evaluation II score	26.2 ± 8.1	4, 54
Infection source, *n* (%)		
Respiratory	1,086 (38.1)	
Gastrointestinal	901 (31.6)	
Urinary tract	295 (10.4)	
Skin and soft tissue	190 (6.7)	
Bloodstream, not catheter related	150 (5.3)	
Bloodstream, catheter related	83 (2.9)	
All other sources	144 (5.0)	
Pre-ICU location, *n* (%)		
Emergency department	1,389 (48.8)	
All other locations	1,460 (51.2)	
Type of admission, *n* (%)		
Nonsurgical	2,268 (79.6)	
Emergency surgery	231 (8.1)	
Elective surgery	350 (12.3)	
Comorbid conditions, *n* (%)		
Diabetes	752 (26.4)	
Immunosuppression unrelated to malignancy	624 (21.9)	
Substance abuse	432 (15.2)	
Chronic renal failure	431 (15.1)	
Chronic obstructive pulmonary disease	400 (14.0)	
Liver failure	240 (8.4)	
Metastatic cancer	269 (9.4)	
Hematologic malignancy	242 (8.5)	
Organic brain disease	165 (5.8)	
No. of organ failures	4.0 ± 1.6	1, 8
Serum lactate, day 1 (mmol/L)	4.3 ± 4.0	0.2, 31.7
Interventions		
Antibiotic timing (hours from onset of shock)[a]	−2.9 ± 27.9	−336.0, 24.0
Median (IQR)	1.9 (0–6.3)	
Vasoactive agent timing (hours from onset of shock)	4.5 ± 4.8	0, 23.8
Median (IQR)	2.8 (1.0–6.3)	
Crystalloids 0–1 hr (L)	0.97 ± 0.89	0, 9.0
Crystalloids 1–6 hr (L)	1.92 ± 1.77	0, 13.0
Crystalloids 6–24 hr (L)	2.69 ± 2.38	0, 15.8

(Continued)

TABLE 1. (*Continued*). Characteristics, Interventions, and Outcomes of 2,849 Patients With Septic Shock

Variable	Value	Range
Colloids 0–1 hr (L)	0.03 ± 0.07	0, 0.8
No. (%) who got any	582 (20.4)	
Colloids 1–6 hr (L)	0.09 ± 0.17	0, 2.8
No. (%) who got any	1,267 (44.5)	
Colloids 6–24 hr (L)	0.19 ± 0.29	0, 3.1
No. (%) who got any	1,664 (58.4)	
Total equivalent volume (L)[b]		
0–1 hr after shock onset	1.02 ± 0.91	0, 9.0
1–6 hr	2.10 ± 1.85	0, 13.3
6–24 hr	3.07 ± 2.54	0, 16.8
Outcomes		
Hospital mortality (%)	47.4	
ICU length of stay (d)	10.9 ± 13.6	1.0, 215.0
Median (IQR)	6.5 (3.1, 13.0)	
Hospital length of stay (d)	27.2 ± 35.2	1.1, 370.0
Median (IQR)	15.0 (6.0, 32.0)	

IQR = interquartile range.
[a]Negative values represent appropriate antibiotics started prior to onset of shock.
[b]Crystalloid volume + (colloid volume × 2).
Values are mean ± SD unless otherwise indicated.

difference, 6.3%; $p = 0.01$) or high volume (median, 3.7 L; mortality difference, 7.5%; $p = 0.002$). The variable with the next largest numerical influence was the timing of vasoactive agents; there were significant differences among the three categories of timing ($p = 0.003$), mortality rates differing by 5.0%, being lowest when given in the 1–6 hours interval.

Regression modeling of the total volume infused during the first 6 hours after onset of hypotension showed that it was highest when vasoactive agents were started 1–2 hours after the onset of shock (**Fig. 1**). Patients who had these agents begun either earlier or later than that received 500–600 mL less resuscitation fluids ($p < 0.0001$).

DISCUSSION

Treatment of hypotension in septic shock usually includes both IV fluids and vasoactive agents (3). Because these two treatments are typically titrated to the same clinical endpoints, it is likely that they exhibit clinically relevant interactions. However, no prior human studies have evaluated their interacting effects. In this multicenter cohort study of severely ill patients with septic shock who survived the initial 24 hours, we evaluated the association between hospital mortality and administration of IV fluids and vasoactive agents during those first 24 hours.

We found that hospital mortality was associated with timing and volume of fluids and with timing of vasoactive agents; complex interactions between these variables were statistically and clinically significant. Absolute hospital mortality associated with the most and least favorable combinations differed by 46%. Although these interactions limit the ability to delineate the independent influence of these variables, a simplified analysis (Table 4) indicated that total fluid volume administered during the 1- to 6-hour interval was the most influential; mortality was 6.3–7.5% higher for patients who received the lowest volume in this interval (median, 0.5 L). There was an apparent plateau effect with no additional benefit with the highest volumes compared to intermediate volumes (median, 3.7 vs 1.7 L; $p = 0.57$). There were also nonsignificant trends to higher mortality if the lowest category of fluid volume (median, 0.3 L) was given in the 0- to 1-hour interval.

Timing of vasoactive drugs was also important. The four fluid/vasoactive combinations with the lowest hospital mortality included large volumes of fluids given early, combined with waiting to begin vasoactive agents until after the initial hour after onset of shock (Table 3). The approximate analysis of the isolated effect of vasoactive drug timing likewise showed significant differences (Table 4) ($p = 0.003$); with higher mortality if these agents were begun more than 6 hours after shock onset, or if they were begun in the first hour. Further understanding of this phenomenon requires appreciation of the complex

TABLE 2. Multivariable Regression Model for Hospital Mortality of 2,849 Patients With Septic Shock

Included in model as multiple variables			
Variable	**Form in Model**	**Direction of Mortality With Higher Values**	***p***
Age	Cubic splines	Increased	< 0.001
Acute Physiology and Chronic Health Evaluation II score	Cubic splines	Increased	< 0.001
Lactate	Cubic splines	Increased	< 0.001
Total equivalent volume 0–1 hr[a]	Categorical	See text, Table 3	
Total equivalent volume 1–6 hr[a]	Categorical	See text, Table 3	
Total equivalent volume 6–24 hr[a]	Categorical	See text, Table 3	
Timing of starting vasoactive agents	Categorical	See text, Table 3	
Included in model as a single variable			
Variable	Form in Model	OR (95% CI)	*p*
Male sex	Binary	0.93 (0.79, 1.09)	0.37
Admission from emergency department (vs any other location)	Binary	0.53 (0.44, 0.65)	< 0.001
Admission type			
Nonsurgical (reference)	Categorical	1.00	Reference
Elective surgery		0.63 (0.46–0.87)	0.005
Emergency surgery		0.93 (0.72–1.19)	0.56
Comorbid conditions			
Liver dysfunction	Binary	2.78 (1.94–3.98)	< 0.001
Hematologic malignancy	Binary	2.24 (1.58–3.18)	< 0.001
Metastatic cancer	Binary	2.09 (1.45–3.00)	< 0.001
Chronic obstructive pulmonary disease	Binary	1.80 (1.45–2.23)	< 0.001
Chronic renal failure	Binary	1.24 (1.05–1.46)	0.01
Immunosuppressed	Binary	1.08 (0.84–1.39)	0.53
Diabetes mellitus	Binary	1.07 (0.82–1.41)	0.61
Substance abuse	Binary	0.85 (0.58–1.26)	0.43
Organic brain disease	Binary	0.80 (0.62–1.03)	0.09
Infection source, *n* (%)			
Respiratory (reference)	Binary	1.00	Reference
Gastrointestinal	Binary	1.11 (0.86, 1.43)	0.42
Urinary tract	Binary	0.42 (0.29, 0.60)	< 0.001
Skin and soft tissue	Binary	0.95 (0.66, 1.36)	0.77
Bloodstream, not catheter related	Binary	0.76 (0.47, 1.21)	0.25
Bloodstream, catheter related	Binary	0.53 (0.30, 0.93)	0.03
All other sources	Binary	2.03 (1.43, 2.86)	< 0.001
No. of organ failures	Linear	1.15 (1.07–1.24)	< 0.001
Year of shock	Linear	0.96 (0.93, 0.99)	0.008

(Continued)

TABLE 2. (*Continued*). Multivariable Regression Model for Hospital Mortality of 2,849 Patients With Septic Shock

Included in model as multiple variables			
Variable	**Form in Model**	**Direction of Mortality With Higher Values**	***p***
Any colloids given 0–1 hr	Binary	1.03 (0.70, 1.51)	0.887
Any colloids given 1–6 hr	Binary	1.24 (0.96, 1.61)	0.099
Any colloids given 6–24 hr	Binary	1.12 (0.90, 1.39)	0.317
Timing of starting appropriate antibiotics			
> 24 hr before shock onset	Categorical	1.43 (1.13–1.81)	0.003
0–24 hr before shock onset		1.12 (0.83–1.50)	0.45
0–4 hr after shock onset		1.00 (reference)	Reference
4–10 hr after shock onset		1.73 (1.39–2.15)	< 0.001
10–24 hr after shock onset		3.61 (2.65–4.91)	< 0.001

OR = odds ratio.
[a]Crystalloid volume + (colloid volume × 2).

interactions between the effects of fluids and vasoactive drugs. This begins with the important finding that, on average, less fluids were given early if vasoactive drugs were begun within the first hour. We speculate that higher blood pressures achieved due to vasoactive agents may lead clinicians to give less fluids; since lower fluid volume was associated with higher mortality, this effect may influence mortality. Furthermore, pharmacologic vasoconstriction in the presence of absolute or relative hypovolemia could further impair organ perfusion, contributing to increased mortality. This latter point aligns with the recognition that the old notion of "cold septic shock" is simply hypoperfusion in patients with a circulating volume insufficient to cope with their dilated capacitance vessels, and that such patients become "warm" after administration of adequate volume of fluids (28).

But, the full model results (Table 3; Appendix Table A1, Supplemental Digital Content 1, http://links.lww.com/CCM/B13) indicate that higher mortality associated with starting vasoactive agents in the initial hour after shock onset is not solely related to the associated tendency to give lower fluid volumes. Demonstrating this are the findings that: 1) the combination of these variables associated with the lowest mortality included high volumes given early, and vasoactive agents begun 1–6 hours after hypotension onset, while 2) the *same* fluid volume categories with vasoactive support begun in the first hour after onset was associated with a significantly higher hospital mortality (46.0% vs 24.7%, $p < 0.0001$). Thus, even with optimal (high) early fluid volumes, very early initiation of vasoactive drugs was associated with worse outcome. Although observational data such as ours do not demonstrate causality, we can speculate that these findings could indicate another, unknown mechanism by which early initiation of vasoconstrictive agents in septic shock may cause harm even in the presence of adequate fluid resuscitation; however, our data do not provide additional insight into such mechanisms.

Although no prior human studies of septic shock evaluated the comparative benefits of increasing blood pressure with fluids versus vasoactive drugs, or the interactions between them, some have assessed fluid resuscitation in sepsis, severe sepsis, and septic shock. A retrospective analysis of 496 patients with sepsis found no association between mortality and the type/volume of fluids, although more fluids were associated with a higher prevalence of heart failure and a lower prevalence of renal failure (4, 10). In two interventional studies in which lower mortality was found for patients randomized to early targeted resuscitation, the volume of fluids administered during the first 6 hours was greater in the intervention arm (10), and in one study, the delay to vasoactive drugs was shorter (5). A meta-analysis of nine studies, including 1,001 sepsis patients, also found lower mortality (odds ratio = 0.64; 95% CI, 0.43–0.96) in patients treated with an early, targeted resuscitation protocol including fluids, inotropes, and vasopressors (5). Our findings of increased mortality in association with late (> 6 hr) initiation of vasoactive agents, low fluid volumes administered during the early period, and late initiation of antibiotics are in keeping with prior studies (4, 21). Similar to our findings, an animal study of endotoxic shock found that early versus later administration of a vasoactive agent was associated with lesser volumes given, but unlike our results, that study found no difference in survival (29). Of note, our findings appear to contradict some prior studies showing worse outcomes with larger volumes of resuscitation fluids in the first 24 hours (30, 31). The reasons for the divergent results are unclear, but our study explicitly included consideration of interactions between fluids and vasoactive drugs, while the other studies did not.

Strengths of our study include a large sample size derived from multiple centers and adjustment for a variety of potentially confounding covariates. It is the first study to simultaneously take account of other therapies used in addition to fluid resuscitation in the management of septic shock, specifically

TABLE 3. Predicted Cohort Hospital Mortality by Timing and Amount of Total Equivalent Volume of Fluids and Timing of Starting Vasoactive Agents, Sorted by Predicted Hospital Mortality, for the 10 Best and 10 Worst Combinations

TEV0–1[a]	TEV1–6[b]	TEV6–24[c]	Vasoactive Drug Timing[d]	Predicted Hospital Mortality (95% CI)
10 Combinations with the lowest mortality				
High	High	Medium	Intermediate	24.7 (9.6, 39.7)
High	Medium	High	Intermediate	32.2 (13.4, 51.0)
Low	High	Low	Intermediate	33.3 (21.7, 44.9)
High	Medium	Low	Intermediate	33.6 (21.0, 46.1)
Medium	High	Medium	Late	35.6 (17.1, 54.0)
Medium	Low	Medium	Early	37.8 (22.7, 52.9)
Medium	Medium	High	Late	37.9 (28.1, 47.8)
Medium	High	Medium	Intermediate	38.2 (25.3, 51.2)
High	High	High	Late	38.4 (29.3, 47.5)
Medium	High	Medium	Early	39.9 (25.8, 53.9)
10 Combinations with the highest mortality				
Medium	Medium	Low	Early	58.6 (43.1, 74.1)
Medium	Low	Low	Late	59.3 (45.8, 72.7)
High	Medium	Low	Early	62.1 (46.9, 77.3)
High	High	Low	Early	62.3 (48.4, 76.2)
Medium	Low	High	Early	63.2 (42.6, 83.8)
Medium	Medium	Low	Late	63.6 (45.6, 81.7)
High	High	Medium	Late	63.7 (49.2, 78.2)
Medium	High	Low	Late	64.9 (45.6, 84.2)
Low	Low	High	Intermediate	67.6 (56.9, 78.2)
High	Low	Medium	Late	71.1 (52.5, 89.6)

TEV = total equivalent volume.
[a]Low: 0–0.50 L, medium: 0.51–1.00 L, high: 1.01–9 L.
[b]Low: 0–1.00 L, medium: 1.01–2.40 L, high: 2.41–13.6 L.
[c]Low: 0–1.62 L, medium: 1.63–3.50 L, high: 3.51–16.8 L.
[d]Early: 0–1 hr; intermediate: 1–6 hr; late: 6–24 hr.
Full modeling results available in Appendix Table A1, Supplemental Digital Content 1, http://links.lww.com/CCM/B13.

the timing of vasoactive drugs and antimicrobials. Our study also has limitations, mainly related to being retrospective and observational. First, recognition of shock may have occurred later than its true time of onset. Second, our data lacked information for some potentially influential variables, such as exact initial blood pressure, the evolution of blood pressure over time, central venous pressure, hemoglobin, and administration of blood products. As a marker of the severity of shock, inclusion of blood pressure in our models would reduce concern about bias by indication, whereby more early fluids and earlier vasoactive agents might simply reflect more severe hypotension, resulting in higher mortality. However, we think such bias is unlikely for three reasons: 1) our model included serum lactate, which may be superior to blood pressure as an indicator of hypoperfusion, 2) instead of an association between more early fluids and increased mortality, our results demonstrate the opposite, and 3) if earlier initiation of vasoactive agents indicated higher severity, then we would have expected it to be associated with more early fluids, but we saw the opposite. Third, in this study, we limited consideration to the starting time of vasoactive agents, and it seems likely that additional details about the dosing, combinations, and duration of these agents would provide further insight into resuscitation in septic shock. However, at the current time, our dataset does not allow us to make these distinctions. Furthermore, even if we did have such information, it would be challenging to include it in our analysis, as the additional layer of interacting variables would multiply concerns about having sufficient sample

TABLE 4. Effects on Hospital Mortality of the Whole Cohort, as Predicted by the Multivariable Model, of Isolated Differences in Vasoactive Agent and IV Fluid Variables

	Predicted Hospital Mortality, % (95% CI)	→Bivariate *p*	Mortality Range (%)
Time of initiating vasoactive agents after onset of shock (hr)		0.003	5.0
0–1	49.6 (45.3, 54.0)	0.08	
1–6	46.7 (43.4, 50.1)	0.30	
6–24	51.7 (48.6, 54.8)	0.0009	
TEV[a] 0–1 hr after onset of shock (L)		0.12	2.9
0–0.50 (median 0.27)	50.1 (46.8, 53.4)	0.066	
0.51–1.00 (median 0.91)	47.1 (42.9, 51.2)	0.13	
1.01–9.00 (median 2.03)	47.5 (44.0, 51.1)	0.81	
TEV[a] 1–6 hr after onset of shock (L)		0.0008	7.5
0–1.00 (median 0.54)	53.1 (48.1, 58.2)	0.01	
1.01–2.40 (median 1.65)	46.8 (43.2, 50.4)	0.002	
2.41–13.60 (median 3.68)	45.6 (42.1, 49.1)	0.57	
TEV[a] 6–24 hr after onset of shock (L)		< 0.0001	3.6
0–1.62 (median 0.83)	50.1 (46.3, 53.7)	< 0.0001	
1.63–3.50 (median 2.49)	46.5 (43.1, 49.9)	0.86	
3.51–16.8 (median 5.24)	49.6 (45.9, 53.4)	0.08	

TEV = total equivalent volume.

[a]TEV = crystalloid volume + (colloid volume × 2).

These mortality and *p* values represent predicted mortality if everyone in our specific cohort had the indicated value of the given variable, keeping all other variables unchanged. Only under strict distributional conditions can these values be generalized to other patient cohorts (see text).

size, even with our relatively large database. Also, it would be increasingly difficult to make sense of interactions among five or more categorized variables. Thus, while our analysis is simplified by not including more details about the vasoactive agents used, these issues lead us to conclude that it will require prospective, interventional studies to sort out these questions. Fourth, our inclusion criteria required hypotension, but did not require any other organ failures. However, in the initial day of septic shock, 99.54% (all but 13 of 2,849 patients) in our analysis cohort had a serum lactate greater than 2.2 mmol/L and/or at least one additional organ failure. Fifth, our findings may not pertain to patients with septic shock who never require vasoactive drugs or those who die within 24 hours of onset because we excluded such individuals to avoid survival bias (24). Fifth, concerns about generalizability arise since, due to missing data elements, 40% of patients with septic shock in this database who met our eligibility requirements were not included in the analysis. Comparison between included and excluded patients (**Appendix Table A2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B13) shows that they differed in a number of ways; most relevant was that excluded patients were less severely ill, received slightly less fluids in all three time intervals, were less likely to have been given colloids, and had lower hospital mortality. And finally, it is important to recognize that our findings regarding the volumes of fluids administered in the three time intervals are group averages; therefore, individualized titration to clinical evidence of perfusion is still indicated.

Regarding our statistical modeling methods, we chose to categorize the fluid and vasoactive drug variables. This not only reduced the complexity of assessing interactions but also reduced our ability to precisely define the optimal volume of fluids or timing of vasoactive agents. A second modeling comment pertains to our choice of independent variables for analysis. This involved a balance because including more potentially influential variables resulted in fewer patients available for analysis due to missing data. For example, excluding serum lactate from the model would have increased the number of patients available for analysis from 2,849 to 4,324. A sensitivity analysis using this larger sample while excluding serum lactate as

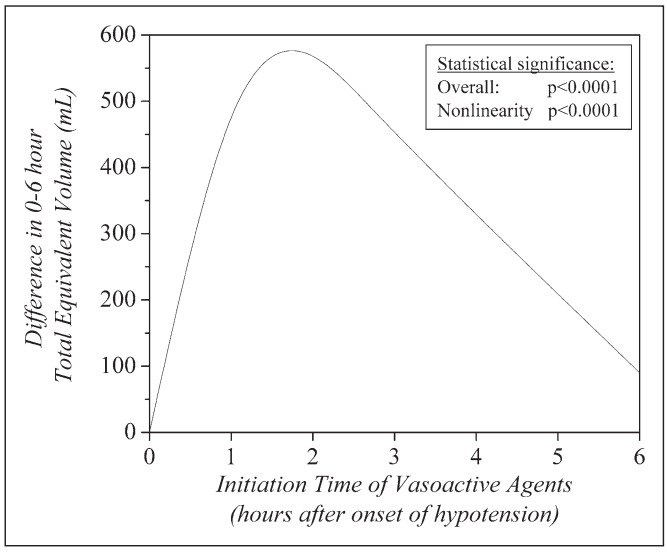

Figure 1. Model-derived association between timing of initiating vasoactive agents and total equivalent volume of fluids (crystalloids + colloids × 2) given 0–6 hr after onset of hypotension among the 2,123 patients with septic shock whose vasoactive agents were begun within 6 hr. *y*-Axis shows average difference in volume administered compared to that provided to patients whose vasoactive agents were begun at the onset of hypotension (time = 0).

an independent variable gave similar results; mortality ranged from 27.9% to 63.3%, with mortality differences of 3.4–5.0% related to independent changes in the fluid and vasoactive drug variables. Finally, our choice of considering the volume effects of colloids to be twice that of isotonic crystalloids could be questioned (10). The results were similar in a sensitivity analysis where we considered their volume effects to be equivalent.

CONCLUSIONS

Although the high prevalence and mortality rates of severe sepsis and septic shock (1, 2) have prompted research into novel therapeutic agents, these approaches have not yet reproducibly improved sepsis survival (32). Consequently, IV fluids, vasoactive agents, and antibiotics remain the mainstays of therapy (3). Our findings support previously shown benefits of aggressive early fluid resuscitation (3, 4). They also suggest that it may be detrimental to start vasoactive agents within the first hour after shock onset, instead delaying them for at least one hour while the fluid resuscitation is begun. We have further highlighted the tendency to administer lower volumes of fluids during the earliest period when blood pressure is raised with vasoactive agents. Because they derive from an observational study, rather than a prospective intervention, our findings are best viewed as hypothesis generating. Although this study is a step toward clarifying the elements of optimal multimodality resuscitation in septic shock, there is a need both for validation of our findings and further work, including prospective interventional studies, to clarify the details of this topic.

ACKNOWLEDGMENT

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