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Moderate IV Fluid Resuscitation Is Associated With Decreased Sepsis Mortality

Keith A. Corl, MD, ScM[1]
Mitchell M. Levy, MD[2]
Andre L. Holder, MD, MS[3,4]
Ivor S. Douglas, MD[5]
Walter T. Linde-Zwirble[6]
Aftab Alam, MD[7]

OBJECTIVES: Significant practice variation exists in the amount of resuscitative IV fluid given to patients with sepsis. Current research suggests equipoise between a tightly restrictive or more liberal strategy but data is lacking on a wider range of resuscitation practices. We sought to examine the relationship between a wide range of fluid resuscitation practices and sepsis mortality and then identify the primary driver of this practice variation.

DESIGN: Retrospective analysis of the Premier Healthcare Database.

SETTING: Six hundred twelve U.S. hospitals.

PATIENTS: Patients with sepsis and septic shock admitted from the emergency department to the ICU from January 1, 2016, to December 31, 2019.

INTERVENTIONS: The volume of resuscitative IV fluid administered before the end of hospital day- 1 and mortality.

MEASUREMENTS AND MAIN RESULTS: In total, 190,682 patients with sepsis and septic shock were included in the analysis. Based upon patient characteristics and illness severity, we predicted that physicians should prescribe patients with sepsis a narrow mean range of IV fluid (95% range, 3.6–4.5 L). Instead, we observed wide variation in the mean IV fluids administered (95% range, 1.7–7.4 L). After splitting the patients into five groups based upon attending physician practice, we observed patients in the moderate group (4.0 L; interquartile range [IQR], 2.4–5.1 L) experienced a 2.5% reduction in risk-adjusted mortality compared with either the very low (1.6 L; IQR, 1.0–2.5 L) or very high (6.1 L; IQR, 4.0–9.0 L) fluid groups $p < 0.01$). An analysis of within- and between-hospital IV fluid resuscitation practices showed that physician variation within hospitals instead of practice differences between hospitals accounts for the observed variation.

CONCLUSIONS: Individual physician practice drives excess variation in the amount of IV fluid given to patients with sepsis. A moderate approach to IV fluid resuscitation is associated with decreased sepsis mortality and should be tested in future randomized controlled trials.

KEYWORDS: intensive care unit; intravenous fluid resuscitation; sepsis; septic shock

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Since IV hypotonic saline mixed with sodium bicarbonate was first administered during the 1832 London cholera pandemic (1), physicians have sought to use IV fluids to restore intravascular circulating volume, improve organ perfusion, and resuscitate critically ill patients. Fluid administration practices used to resuscitate patients with sepsis have evolved over time, with significant changes in clinical practice occurring over the last three decades. Following the publication of the Rivers trial in 2001, the apparent benefit of early goal-directed therapy made high-volume IV fluid resuscitation widely popular for patients with sepsis and septic shock (2). The evolution in the resuscitation culture from a relatively low-volume to a high-volume strategy

KEY POINTS

Question: Current research suggests equipoise between a tightly restrictive or more liberal resuscitation strategy for patients with sepsis but data is lacking on a wider range of resuscitative practices.

Findings: In this retrospective analysis of 190,682 ICU patients with sepsis and septic shock, we found that being resuscitated by a physician who on average uses a moderate amount of IV fluid on the first day of care is associated with reduced mortality (2.5% lower) compared with patients resuscitated with either a very low or very high volume of IV fluid.

Meaning: A moderate approach to IV fluid is associated with decreased sepsis mortality and should be tested in future randomized controlled trials.

was swift. Throughout the 2000s, it was not uncommon for patients with sepsis to receive more than 10 L of IV fluid within the first 24 hours of care. Not long thereafter observational studies associated positive fluid balances with increased rates of respiratory failure and mortality (3–5). In the early 2010s, with growing concern that high-volume resuscitation was causing harm, there was a reevaluation of what had become accepted dogma (6–8). Clinical uncertainty surrounding the optimal IV fluid resuscitation strategy lead to large practice variation between physicians and hospitals (9). This phenomena is observed both in sepsis and in a variety of medical conditions across specialties (10, 11). Some physicians continued to employ high-volume fluid resuscitation while others adopted a more restrictive approach, giving less than the Surviving Sepsis Campaign's recommended 30 mL/kg fluid bolus (12). Two large randomized controlled trials (RCTs) published in 2022 and 2023 compared a restrictive vs. liberal IV fluid management strategy for patients with sepsis associated hypotension (13, 14). Neither study demonstrated a benefit in mortality, use of vasopressors, or mechanical ventilation for either approach.

We characterized and then examined the relationship between a broad range of IV fluid resuscitation practices during the first day of hospitalization and mortality among patients with sepsis and septic shock admitted to the ICU using data from the Premier Healthcare Database. We then examined the extent to which the observed variability in IV fluid resuscitation practices were explained by physician variation within a given hospital vs. differences in care between hospitals.

METHODS

Data Source and Study Sample

We acquired de-identified data (blinded to patients, physicians, and hospitals) from the Premier Healthcare Database from January 1, 2016, to December 31, 2019, the 4-year period immediately before the COVID-19 pandemic. The database includes detailed billing data of approximately 20% of U.S. hospitals (15). Given the use of de-identified data exclusively, this study was deemed not to require internal review board review based upon the policy of National Institutes of Health, under the revised Common Rule. We included patients with *International Classification of Diseases*, 10th Revision, Clinical Modification (ICD-10-CM) codes for sepsis and septic shock as well as patients coded for infection with acute organ dysfunction present on admission (POA) (16). We refer to severe sepsis as sepsis throughout the article since it was reclassified in the 2016 Sepsis-3 definitions (17). Further enrollment criteria included: age 18 years old or older, admission from the emergency department to the ICU on hospital day-1, and receipt of parenteral antibiotics and IV fluids on day-1. Hospital day-1 was defined as the first day of record with a hospital room charge. IV fluids received in the emergency department before hospital day-1 (11% of patients) were included in the day-1 fluid total. Exclusion criteria were grouped among the following categories: hospital, patient, or IV fluid based. We excluded hospitals with less than 20 cases due to limitations in analyzing small sample sizes and hospitals where greater than 25% of cases received less than 500 mL of IV fluid on day-1, as this likely represents fluid underreporting at the hospital level. We excluded patients with a "do not resuscitate" order as we believed this might bias physicians to limit IV fluid resuscitation, patients who underwent surgery, and patients who received less than 1000 mL of day-1 IV fluids as this likely does not reflect usual practice. We excluded patients transferred from another hospital with the assumption that fluid resuscitation occurred at the referring hospital. We excluded IV fluid volumes

of less than 500 mL as this likely represents carrier fluid administered with medications and any hypotonic dextrose solutions (**Fig. S1**, http://links.lww.com/CCM/H573). For a detailed list of ICD-10-CM codes used to define patient demographics, characteristics, organ dysfunction, and comorbidities, see **Table S1** (http://links.lww.com/CCM/H573).

Measures

The primary outcome was hospital mortality. The primary independent variable was the attending fluid group based upon resuscitative IV fluid administered before the end of hospital day-1 ($IVFD_1$). Secondary outcomes were use of vasopressors, mechanical ventilation, diuretics, and the initiation of new hemodialysis (**Table S2**, http://links.lww.com/CCM/H573).

Statistical Analysis

We performed multivariable linear regression that included an analysis of variance to predict the mean amount of $IVFD_1$ patients should have received based upon patient characteristics POA. These factors included: patient demographics (age and sex), conditions that trigger IV fluid resuscitation (electrolyte disorders and acute organ dysfunctions), and factors that prompt withholding IV fluid resuscitation (end-stage renal disease, heart failure, chronic bronchitis, and pulmonary hypertension) (**Supplemental Methods** and **Table S3**, http://links.lww.com/CCM/H573). We then used output from this model to examine the attending physician mean residual (observed–expected) $IVFD_1$. We assigned the physicians by increasing mean residual $IVFD_1$ into nine equally sized groups. Following inspection, we reduced the groups to five attending fluid groups to make the difference in $IVFD_1$ between groups clinically meaningful: very low (11%), low (22%), moderate (33%), high (22%), and very high (11%) (**Fig. S2**, http://links.lww.com/CCM/H573).

For our primary and secondary analyses, we used logistic regression to determine the risk of our outcomes for each attending group adjusted for previously validated patient demographics and the severity of illness POA (5) (Table S2, http://links.lww.com/CCM/H573). To create the lower and higher severity patient subgroups, we ordered the patients in ascending risk of predicted hospital mortality and split the cohort equally (**Fig. S3**, http://links.lww.com/CCM/H573). In subgroup analyses, we compared outcomes for patients who did and did not require vasopressors on hospital day-1 as well as for patients with congestive heart failure, end-stage renal disease, and pulmonary hypertension POA. We then compared primary and secondary outcomes between the fluid groups using the Student *t* test.

To examine whether differences in mortality associated with $IVFD_1$ were attributed to physician practices within a given hospital or differences between hospitals, we constructed a fixed-effects logistic regression model that included the hospital identification number as well as the patient variables included in our primary analysis. A flowchart outlining the statistical approach is provided (**Fig. S4**, http://links.lww.com/CCM/H573). Databases were constructed in FoxPro (Microsoft Corp, Redmond, WA), all statistical analyses were performed in Data Desk (Data Description, Ithaca, NY).

RESULTS

Patient Characteristics

Our study sample included 190,682 patient admissions for sepsis (47%) and septic shock (53%), cared for by 24,445 attending physicians across 612 hospitals in the United States. Baseline patient characteristics were similar between fluid groups (**Table 1**). Patients in the higher severity group had a higher rate of septic shock, organ dysfunction, and malignant neoplasm compared with the lower severity group.

Examining hospital characteristics, patients who were treated in the moderate fluid group were more likely to have received care at a medium size hospital (200–299 beds) and/or in the South. Patients who received care at larger hospitals (500+ beds) and/or were in the West were more likely to receive a very low $IVFD_1$, whereas patients in the Northeast were more likely to receive a very high $IVFD_1$ (**Table S4**, http://links.lww.com/CCM/H573).

IV Fluid Resuscitation Variation

Controlling for baseline patient characteristics, the model predicted that physicians should have administered a narrow mean range of $IVFD_1$ (95% range, 3.6–4.5 L; **Fig. 1*A***). Instead, we observed a wide variation of mean $IVFD_1$ in clinical practice (95% range, 1.7–7.4 L).

TABLE 1.
Patient Characteristics

Characteristic	Attending Fluid Group					Patient Severity Group	
	Very Low	Low	Moderate	High	Very High	Lower	Higher
Cases, *n*	21,079	42,291	63,557	42,554	21,201	94,505	96,177
Male, %	52.2	50.8	50.8	51.1	51.2	48.3	53.8
Mean age, yr	65	66	66	65	66	62	69
Organ dysfunction present at admission, %							
Septic shock	57.4	53.8	51.8	51.4	50.3	33.8	71.1
Renal	55.3	53.4	52.9	53.2	52.9	34.9	71.4
Respiratory	43.6	42.3	41.9	42.9	44.0	24.0	60.9
CNS	31.5	30.2	29.9	30.9	31.1	16.9	43.8
Hepatic	5.8	4.8	4.5	4.8	5.0	0.1	9.5
Number of systems, mean	2.1	2.0	2.0	2.0	2.0	1.2	2.8
Site of infection, %							
Respiratory	46.3	47.8	48.8	47.4	46.9	49.4	46.2
Genitourinary	26.6	28.1	27.5	26.8	26.3	26.1	28.4
Abdominal	6.9	6.8	6.4	6.5	6.4	6.0	7.1
Endocarditis	1.6	1.5	1.3	1.3	1.5	1.6	1.2
CNS	1.7	1.4	1.3	1.5	1.4	1.4	1.4
Skin/soft tissue	1.5	1.3	1.2	1.3	1.3	1.4	1.2
Device related	1.1	0.8	0.7	0.8	1.0	0.9	0.7
Comorbidities, %							
Electrolyte disorders	72.6	71.3	70.7	70.4	70.6	64.1	77.7
Congestive heart failure	30.0	31.7	32.4	32.4	33.2	28.1	35.9
Chronic kidney disease	28.2	29.6	29.1	28.9	28.6	23.4	34.5
Chronic obstructive pulmonary disease	29.5	31.4	33.2	31.8	32.3	35.3	28.7
Diabetes	17.9	19.1	19.4	19.2	19.2	17.3	20.8
Neoplasm	11.0	11.3	10.8	10.5	10.7	4.1	17.5
Metastatic neoplasm	5.1	5.2	4.8	4.6	4.8	0.7	9.0
Liver disease	12.2	10.9	10.2	10.4	10.1	4.4	16.7
Dementia	7.7	8.1	7.6	7.5	8.1	5.5	10.0
Paraplegia or quadriplegia	2.2	2.3	2.1	2.2	2.2	2.5	1.9
Number of comorbidities, mean	2.2	2.2	2.2	2.2	2.2	1.9	2.5

Authors' analysis of data provided by the Premier Healthcare Database. All differences between attending fluid groups were significant ($p < 0.01$). Organ dysfunction, site of infection, and baseline comorbidities are not mutually exclusive.

Physicians in the moderate fluid group administered a median 4.0 L $IVFD_1$ (interquartile range [IQR], 2.4–5.1 L) compared with 1.6 L (IQR, 1.0–2.5 L) in the very low, 3.0 L (IQR, 2.0–4.0 L) in the low, 4.5 L (IQR, 3.0–6.1 L) in the high, and 6.1 L (IQR, 4.0–9.0 L) in the very high group ($p < 0.01$ for all groups compared with the moderate group). Physicians in the very low fluid group administered 2.2 L less, and physicians in the very high group administered 2.9 L more than what the model predicted they should have given on average (**Table 2**). **Figure 1*B*** and **Table S5** (http://links.lww.com/CCM/H573) further characterize the wide

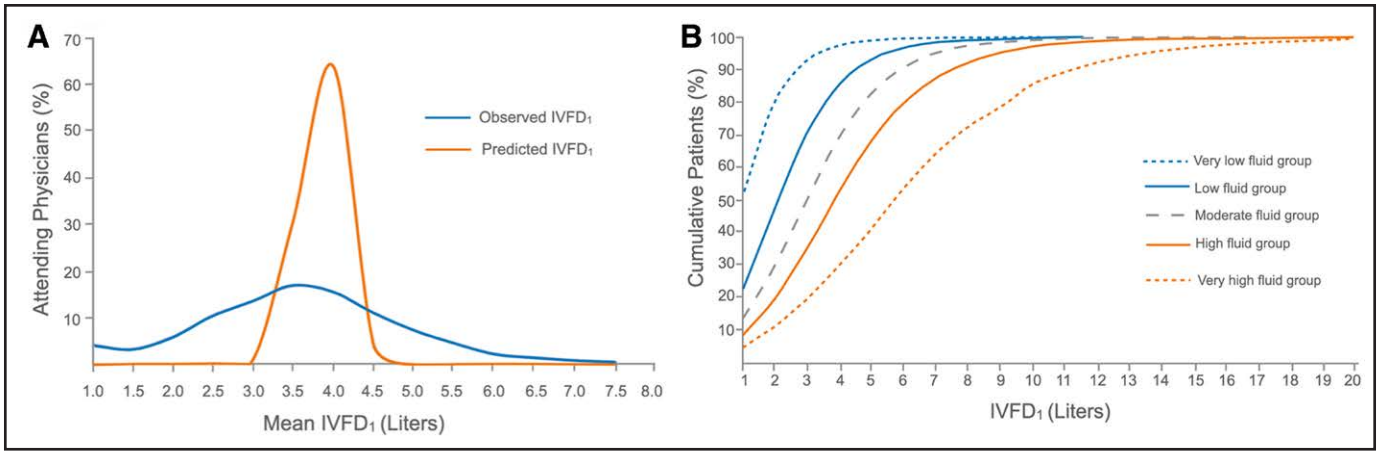

Figure 1. Variation in resuscitative IV fluid administered within the first day. **A**, Observed and mean predicted volume of IV fluid administered before the end of hospital day-1 ($IVFD_1$) based upon baseline patient characteristics. Patient demographic and illness severity variables included in the $IVFD_1$ prediction model are displayed in Table S3 (http://links.lww.com/CCM/H573). **B**, Cumulative number of patients within attending fluid groups by increasing amounts of $IVFD_1$. Table S5 (http://links.lww.com/CCM/H573) further describes $IVFD_1$ volumes by attending fluid group.

variation in $IVFD_1$ between physician fluid groups. For example, we observed that 80% of patients in the very low fluid group received less than or equal to 2.0 L $IVFD_1$, whereas 46% of patients in the very high fluid group received greater than 6.0 L of $IVFD_1$ and 10% received greater than or equal to 11.0 L.

Sepsis Mortality and Secondary Outcomes

Patients who received care from physicians in the moderate fluid group experienced a reduced adjusted mortality compared with all other fluid groups: –2.5% vs. very low, –1.4% vs. low, –0.5% vs. high, and –2.5% vs. very high ($p < 0.01$ vs. very low, low, and very high; $p = 0.06$ vs. high). These observed differences in mortality persisted, but were smaller for the lower severity and sepsis without day-1 vasopressors subgroups, and were larger for those in the higher severity and sepsis with day-1 vasopressors (Table 2; and **Table S6** and **Figs. S5** and **S6**, http://links.lww.com/CCM/H573). Analyses that examined risk-adjusted mortality each day (days 1–8) showed that the mortality benefit associated with the moderate fluid group was present at the completion of day-1 and increased each day until day 6, after which the mortality benefit persisted but did not increase in magnitude (**Table S7**, http://links.lww.com/CCM/H573). Physicians in the moderate group administered less median $IVFD_1$ to patients with preexisting congestive heart failure (3.1 L), end-stage renal disease (2.6 L), and pulmonary hypertension (3.0 L) POA compared with the total cohort (4.0 L). Patients within these groups experienced reduced mortality compared with the very low or very high fluid groups (**Fig. S7**, http://links.lww.com/CCM/H573).

We observed that patients in the moderate fluid group required a lower risk-adjusted rate of mechanical ventilation: –5.8% vs. very low, –2.7% vs. low, –1.2% vs. high, and –5.1% vs. very high during the first day of care ($p < 0.01$ for all comparisons). This finding persisted across both lower and higher severity groups, among patient subgroups that did/did not require vasopressors on day-1, and patients with congestive heart failure, end-stage renal disease, and pulmonary hypertension POA. We observed that physicians who administered a very low or low $IVFD_1$ did not prescribe higher risk-adjusted rates of vasopressors, while physicians who administered very high $IVFD_1$ did prescribe more vasopressors (Table 2 and **Fig. 2**).

Within- and Between-Hospital Differences in Sepsis Mortality

A partitioning of the sum of squares analysis found that the amount of variation explained by physician practice was approximately four times the amount explained by patient characteristics alone. Using a fixed-effects regression model, which controlled for unmeasured confounding between hospitals, we observed that the mortality benefit associated with the moderate fluid group was largely preserved (**Fig. 3**). Differences in resuscitation practices between hospitals may account for a small portion of the variation in $IVFD_1$ noticeable in

TABLE 2.
Day 1 Fluid Use and Outcomes by Attending Fluid Group

IV Fluid/Interventions	Attending Fluid Group					Total Cohort (*n* = 190,682)
	Very Low (*n* = 21,079)	Low (*n* = 42,291)	Moderate (*n* = 63,557)	High (*n* = 42,554)	Very High (*n* = 21,201)	
$IVFD_1$ total, L, median (IQR)	1.6 (1.0–2.5)[a]	3.0 (2.0–4.0)[a]	4.0 (2.4–5.1)	4.5 (3.0–6.1)[a]	6.1 (4.0–9.0)[a]	3.5 (2.0–5.1)
Mean (SD)	2.0 (± 1.1)[a]	3.0 (± 1.7)[a]	3.9 (± 2.1)	4.9 (± 2.6)[a]	6.9 (± 3.9)[a]	4.1 (± 2.7)
Lower severity, median (IQR)	1.5 (1.0–2.5)[a]	2.6 (2.0–4.0)[a]	3.5 (2.1–5.0)	4.1 (3.0–6.0)[a]	6.0 (4.0–8.5)[a]	3.2 (2.0–5.5)
Mean (SD)	1.9 (± 1.0)[a]	2.9 (± 1.6)[a]	3.7 (± 2.0)	4.6 (± 2.5)[a]	6.6 (± 3.8)[a]	3.9 (± 2.6)
Higher severity, median (IQR)	2.0 (1.0–2.5)[a]	3.0 (2.0–4.1)[a]	4.0 (2.6–5.1)	5.0 (3.1–6.5)[a]	7.0 (4.5–9.5)[a]	4.0 (2.1–5.5)
Mean (SD)	2.0 (± 1.1)[a]	3.2 (± 1.7)[a]	4.1 (± 2.1)	5.1 (± 2.6)[a]	7.3 (± 4.0)[a]	4.2 (± 2.8)
Normal saline, %	87[a]	89[a]	92	91[b]	91[b]	90
Lactate ringers, %	13[a]	11[a]	8	9[a]	9[a]	10
Predicted $IVFD_1$, L, mean	4.1	4.1	4.0	4.0	4.0	4.0
Observed–predicated $IVFD_1$	−2.2	−1.0	−0.1	0.8	2.9	0.0
Steroids, %	30.2[a]	30.2[a]	32.0	32.0	35.7[b]	31.8
Outcomes						
Risk-adjusted mortality, %						
Total cohort	20.0[a]	18.9[a]	17.5	18.0[c]	20.0[a]	18.5
Lower severity	10.2[a]	9.9[a]	9.0	9.3	11.0[a]	9.6
Higher severity	29.5[a]	27.7[a]	25.8	26.5	28.8[a]	27.1
ICU length of stay, d, mean (SD)	5.3 (± 5.5)[a]	5.3 (± 5.8)[a]	5.9 (± 5.8)	5.0 (± 5.4)	4.6 (± 5.4)[a]	5.1 (± 5.5)
Hospital length of stay, d, mean (SD)	9.3 (± 10.7)[a]	9.3 (± 9.4)[a]	9.0 (± 8.8)	9.2 (± 9.7)[b]	8.1 (± 9.7)[a]	9.1 (± 9.4)
Cost, ×$1,000, mean (SD)	27.4 (± 32.0)[a]	27.2 (± 30.4)[a]	25.7 (± 30.1)	27.1 (± 29.2)[a]	29.3 (± 29.9)[a]	27.0 (± 30.2)
Day 1 interventions						
Risk-adjusted vasopressors, %						
Total cohort	47.0	45.9[a]	47.0	47.9[a]	53.1[a]	47.6
Lower severity	34.9	33.1[a]	34.6	35.1	40.1[a]	35.0
Higher severity	59.0	58.4	59.2	60.6[a]	65.9[a]	60.1
Risk-adjusted mechanical ventilation, %						
Total cohort	47.2[a]	44.2[a]	42.0	42.8[b]	47.7[a]	43.9
Lower severity	43.8[a]	41.4[a]	38.6	38.4	44.1[a]	40.3
Higher severity	50.6[a]	47.0[a]	45.3	47.2[a]	51.2[a]	47.4

(*Continued*)

TABLE 2. (*Continued*)

Day 1 Fluid Use and Outcomes by Attending Fluid Group

IV Fluid/Interventions	Attending Fluid Group					Total Cohort (*n* = 190,682)
	Very Low (*n* = 21,079)	Low (*n* = 42,291)	Moderate (*n* = 63,557)	High (*n* = 42,554)	Very High (*n* = 21,201)	
Hospital interventions						
Risk-adjusted vasopressors, %						
Total cohort	60.5	59.9	60.4	60.6	63.7[a]	60.8
Lower severity	47.0	46.1	46.9	46.7	50.3[a]	47.1
Higher severity	73.8	73.5	73.6	74.3	76.8[a]	74.1
Risk-adjusted mechanical ventilation, %						
Total cohort	58.9[a]	55.8[a]	53.1	54.3[a]	58.2[a]	55.2
Lower severity	54.7[a]	52.2[a]	49.1	49.0	53.8[a]	50.9
Higher severity	63.1[a]	59.3[a]	57.0	59.5[a]	62.6[a]	59.4
Risk-adjusted receipt of diuretics,%						
Total cohort	49.2[a]	49.4[a]	50.7	51.2	52.6[a]	50.6
Lower severity	45.6	45.1[a]	46.8	47.2	49.4[a]	46.7
Higher severity	52.7[a]	53.6[a]	54.6	55.2	55.8	54.5
Risk-adjusted new hemodialysis, %						
Total cohort	4.4	4.4	4.4	4.6	5.0[a]	4.5
Lower severity	2.3	1.8[a]	2.1	2.1	2.3	2.1
Higher severity	6.5	6.9	6.6	7.0	7.7[a]	6.9

IQR = interquartile range, $IVFD_1$ = IV fluid administered before the end of hospital day-1.

[a]$p < 0.01$ for values compared with moderate fluid group.

[b]$p \leq 0.05$ for values compared with moderate fluid group.

[c]$p = 0.06$ for values compared with moderate fluid group.

$IVFD_1$ volumes were unadjusted. Predicted $IVFD_1$ was calculated based upon a model including patient demographic illness severity variables listed in Table S3 (http://links.lww.com/CCM/H573). Day- 1 and hosptial outcomes are further detailed in **Figures S5** and **S10** (http://links.lww.com/CCM/H573). Mortality and secondary outcomes were adjusted by the covariates listed in the *Text*.

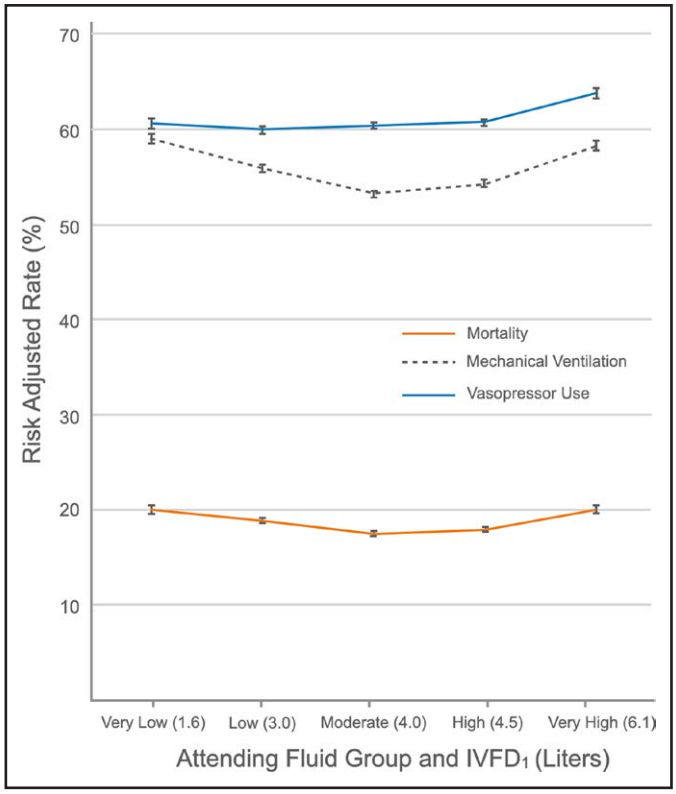

Figure 2. Risk-adjusted hospital mortality, mechanical ventilation, and vasopressor use by attending fluid group. Hospital mortality, mechanical ventilation, and vasopressor use were adjusted by the covariates listed in the *Text*. Resuscitative IV fluid administered before the end of hospital day-1 ($IVFD_1$).

the very low and very high fluid groups. An additional analysis observed that the presence of patient characteristics that might either trigger or prompt withholding of IV fluid resuscitation accounted for only a small difference in the amount of $IVFD_1$ administered between fluid groups. Physician behavior, independent of patient characteristics, accounted for the majority of the difference in $IVFD_1$ administered between fluid groups (**Fig. S8**, http://links.lww.com/CCM/H573).

DISCUSSION

We examined physician and hospital IV fluid resuscitation practices for patients with sepsis and septic shock using the Premier Healthcare Database. We found that while baseline patient characteristics predict that patients with sepsis should receive a relatively narrow range of mean IV fluids on day-1 (95% range, 3.6–4.5 L), in practice they received a much wider range (95% range, 1.7–7.4 L). Our findings indicate that being treated by a physician who on average administers a moderate amount of $IVFD_1$ (4.0 L; IQR, 2.4–5.1 L) is associated with decreased mortality. Moderate $IVFD_1$ is also associated with decreased rates of mechanical ventilation, vasopressor use, and new hemodialysis. Contrary to current recommendations to initiate vasopressors early (18) and the common practice of using early vasopressors to reduce resuscitation volumes (19), we did not observe increased utilization of vasopressors in the lower fluid groups despite increased mortality rates. This may reflect a component of clinical mismanagement as physicians who intentionally adopt a low fluid resuscitation strategy typically supplement fluid with vasopressors to achieve mean arterial pressure resuscitation targets. In a subgroup analysis of patients with baseline heart failure, end-stage renal disease, and pulmonary hypertension, resuscitation with a median of 2–3 L of $IVFD_1$ is associated with reduced mortality compared with lower or higher $IVFD_1$. This is consistent with prior work, which demonstrated septic patients with preexisting heart and renal failure experienced reduced mortality following implementation of a sepsis bundle that mandated a bolus of 30 mL/kg compared with lower volumes of $IVFD_1$ (20). Finally, an analysis that accounted for within- and between-hospital differences found that most of the observed variation in $IVFD_1$ is attributed to within-hospital physician variation. Physician behavior, independent of patient characteristics that might either trigger IV fluid resuscitation or prompt withholding of IV fluid, accounts for the majority of variation in $IVFD_1$ practices observed between fluid groups.

Our findings add context to and extend the work of the 2023 "Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension (CLOVERS)" trial (14) and a subsequent meta-analysis (21), which showed no benefit to either a restrictive or liberal fluid resuscitation strategy for patients with sepsis. Of the existing RCTs, CLOVERS, which enrolled patients early in the emergency department and followed them for the first 24 hours in the ICU, most closely resembles our study population. CLOVERS was powered to detect at 4.5% absolute mortality reduction but observed no significant difference (14.0 vs. 14.9%) between study arms. The trial protocol resulted in the restrictive arm receiving a median of 3.3 L and the liberal arm 5.5 L of IV fluid

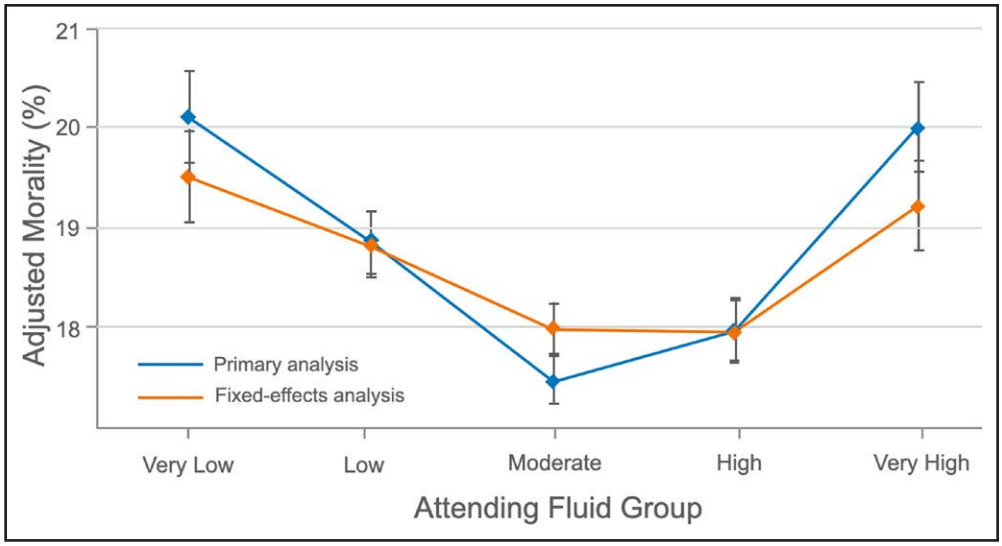

Figure 3. Risk-adjusted mortality controlling for variations in care between hospitals. This figure's results were based upon a fixed-effects logistic regression, in which the 612 hospitals were entered into the model with the covariates used in the primary analysis. A result in which the observed differences in adjusted mortality between fluid groups were entirely a result of between-hospital differences would be represented by a *horizontal fixed-effects line*.

(combined pre- and post-randomization) within the first day. While our overall cohort mortality rate of 18.5% is higher than that of CLOVERS, our findings predict that no significant mortality difference would be observed comparing 3.3 vs. 5.5 L of $IVFD_1$. These volumes are on equivalent and opposite sides of our U-shaped mortality curve (Fig. 3; and **Fig. S9**, http://links.lww.com/CCM/H573). Our observed mortality rates suggest that a trial would require more than 7680 study participants (assuming 80% power and 95% confidence) to detect a 2.5% difference in mortality between fluid groups. Nevertheless, given the large global heath burden of sepsis and the relatively low numbers needed to treat to prevent a mortality, such a trial is needed (**Table S8**, http://links.lww.com/CCM/H573) (22).

Our study has three main clinical practice and research implications. First, the increased mortality rates associated with the very low fluid group support the Surviving Sepsis Campaign's recommended 30 mL/kg IV fluid bolus. While physicians should always consider a patient's individual clinical circumstances, our data suggests that very few should receive less than 2.0 L of $IVFD_1$. This is consistent with the CLOVERS trial, in which the restrictive arm received a mean of 3.3 L of fluids over the first 24 hours of care. Patients with congestive heart failure, end-stage renal disease, and pulmonary hypertension should receive a lower amount of $IVFD_1$ (median, 2–3 L) compared with septic patients without these comorbidities. Our data also suggest a patient-dependent upper bound in $IVFD_1$, above which additional resuscitation is associated with increased mortality for all patients. This is consistent with artificial intelligence sepsis models that have examined IV fluid resuscitation and sepsis mortality (23). Second, the observed within- and between-hospital analysis suggests that the excess variation in $IVFD_1$ associated with increased mortality is mostly attributed to physician variation rather than differences in care between hospitals. Critical care guidelines, hospitals, and institutions should target reducing physician variation in IV fluid administration with sepsis resuscitation educational programs and pre-populated sepsis IV fluid ordering sets that suggest both minimum and maximum fluid limits. Third, the reported mortality effects and $IVFD_1$ volumes should be considered for planning future RCTs. Until comparison between more disparate fluid groups are prospectively tested, physicians should avoid giving volumes of $IVFD_1$ less than 2.0 L or more than 5.0 L to most ICU patients with sepsis.

Our study has limitations. First, the observational study design could not establish a causal relationship between $IVFD_1$ and sepsis mortality. While our study design is susceptible to confounding by indication, if significant confounding by indication existed we would expect to observe decreased instead of increased mortality in the very low and low fluid groups. Second, the Premier Database lacked detailed data on the time to or appropriateness of antibiotics, which have been associated with improved sepsis outcomes (24, 25). These and other unmeasured variables such as organism virulence, time to source control, and concomitant drivers of shock may have contributed to study confounding. Third, using ICD-10 coding methods have been shown to under report sepsis prevalence (26). While coding variation

exists between hospitals, the range in the performance of ICD-10 sepsis case identification varies widely (27). We attempted to mitigate this effect by including patients coded for infection with acute organ dysfunction as well as patients coded with sepsis at admission. In addition, using ICD-10 codes to identify baseline comorbidities will inherently capture a spectrum of disease. It is possible that while the frequencies of diseases processes between fluid groups often appear similar, our modeling approach may not have fully controlled for confounding by illness severity. Fourth, our data lacked patient weights and heights. We, therefore, could not report weight-adjusted $IVFD_1$ volumes. Fifth, less than three percent of hospitals reported data on the use of invasive or noninvasive hemodynamic monitoring to individually tailor IV fluids, and the Premier Database lacks data on patient clinical signs or hospital processes used to direct fluid management. Hemodynamic-directed, patient-tailored IV fluid resuscitation has been shown to avoid excess IV fluid administration (28) and may decrease sepsis mortality (29). It is possible that greater use of patient-tailored fluid resuscitation might lead to different practices and improved outcomes.

CONCLUSIONS

We found that there is a wide variation in the amount of resuscitative IV fluid administered to patients with sepsis and septic shock and that being treated by a physician who administers on average a moderate amount of $IVFD_1$ is associated with decreased mortality. This variation in IV fluid resuscitation is most attributed to within-hospital differences in physician practice rather than differences in resuscitation practices between hospitals. Unless clinical circumstances dictate a different practice, our data suggest adopting a moderate approach to IV fluid resuscitation, one that avoids either extreme of tightly restricting or aggressively administering IV fluid for patients with sepsis and septic shock. Future randomized controlled trials based on our observations are warranted.

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1 *Division of Pulmonary Critical Care, Kaiser Permanente, Modesto, CA.*

2 *Division of Pulmonary, Critical Care, and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.*

3 *Department of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University School of Medicine, Atlanta, GA.*

4 *Emory Critical Care Center, Atlanta, GA.*

5 *Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz School of Medicine, Aurora, CO.*

6 *ZD Associates LLC, Perkasie, PA.*

7 *Baxter International, Deerfield, IL.*

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Dr. Corl was involved in study design, data interpretation, drafting, and revision of article. Drs. Levy, Holder, and Douglas were involved in data interpretation, drafting, and revision of article. Drs. Linde-Zwirble and Alam were involved in study design, data interpretation, drafting, and revision of article.

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For information regarding this article, E-mail: keithcorlmd@gmail.com

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