Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis*

Karthik Raghunathan, MD, MPH[1,2]; Andrew Shaw, MB, FRCA, FFICM, FCCM[1]; Brian Nathanson, PhD[3]; Til Stürmer, MD, PhD[4]; Alan Brookhart, PhD[4]; Mihaela S. Stefan, MD[5]; Soko Setoguchi, MD, DrPH[6]; Chris Beadles, MD, PhD[2]; Peter K. Lindenauer, MD, MSc[7]

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[1]Depawwrtment of Anesthesiology, Duke University Medical Center, Durham, NC.

[2]Durham VA Medical Center, Durham, NC.

[3]OptiStatim LLC, Longmeadow, MA.

[4]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

[5]Department of Medicine, Baystate Medical Center, Springfield, MA.

[6]Department of Medicine, Duke University School of Medicine, Durham, NC.

[7]Center for Quality of Care Research and Department of Medicine, Baystate Medical Center and Tufts University School of Medicine, Springfield, MA.

This study was performed at Duke University, University of North Carolina Chapel Hill, Baystate Medical Center, and OptiStatim LLC.

Drs. Raghunathan, Shaw, Nathanson, and Lindenauer were involved in the conception, hypothesis delineation, design of the study, and acquisition of the data. Dr. Nathanson conducted the data analysis. All authors were involved in the analysis and interpretation of such information and were involved in writing the article or substantially involved in revisions prior to submission. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. No individuals contributing to data collection, analysis, writing or editing assistance, and review of manuscript have been omitted.

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Address requests for reprints to: Karthik Raghunathan, MD, MPH, Department of Anesthesiology, Duke University Medical Center/Durham VAMC, DUMC 3094, Durham, NC 27710. E-mail: karthik.raghunathan@duke.edu

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Objective: Isotonic saline is the most commonly used crystalloid in the ICU, but recent evidence suggests that balanced fluids like Lactated Ringer's solution may be preferable. We examined the association between choice of crystalloids and in-hospital mortality during the resuscitation of critically ill adults with sepsis.

Design: A retrospective cohort study of patients admitted with sepsis, not undergoing any surgical procedures, and treated in an ICU by hospital day 2. We used propensity score matching to control for confounding and compared the following outcomes after resuscitation with balanced versus with no-balanced fluids: in-hospital mortality, acute renal failure with and without dialysis, and hospital and ICU lengths of stay. We also estimated the dose-response relationship between receipt of increasing proportions of balanced fluids and in-hospital mortality.

Setting: Three hundred sixty U.S. hospitals that were members of the Premier Healthcare alliance between November 2005 and December 2010.

Patients: A total of 53,448 patients with sepsis, treated with vasopressors and crystalloids in an ICU by hospital day 2 including 3,396 (6.4%) that received balanced fluids.

Interventions: None.

Measurements and Main Results: Patients treated with balanced fluids were younger and less likely to have heart or chronic renal failure, but they were more likely to receive mechanical ventilation, invasive monitoring, colloids, steroids, and larger crystalloid volumes (median 7 vs 5 L). Among 6,730 patients in a propensity-matched cohort, receipt of balanced fluids was associated with lower in-hospital mortality (19.6% vs 22.8%; relative risk, 0.86; 95% CI, 0.78, 0.94). Mortality was progressively lower among patients receiving larger proportions of balanced fluids. There were no significant differences in the prevalence of acute renal failure (with and without dialysis) or in-hospital and ICU lengths of stay.

Conclusions: Among critically ill adults with sepsis, resuscitation with balanced fluids was associated with a lower risk of in-hospital mortality. If confirmed in randomized trials, this finding could have significant public health implications, as crystalloid resuscitation is nearly universal in sepsis. (*Crit Care Med* 2014; 42:1585–1591)

Key Words: balanced fluids; crystalloids; isotonic saline; mortality; resuscitation; sepsis

Sepsis is defined as the presence of presumed or proven infection with systemic inflammatory manifestations (1). Severe sepsis implies the additional presence of acute organ dysfunction, whereas septic shock is sepsis with persistent hypotension despite adequate fluid resuscitation (1, 2). In the United States, hospitalization for severe sepsis may involve nearly 750,000 patients annually, and although mortality rates are declining, the prevalence is increasing (3, 4). More than one in four hospitalized patients still dies, far more than myocardial infarction or stroke (4, 5). Guidelines recommend early resuscitation with IV crystalloids to restore effective circulating volume (grade 1B) (1) and large amounts are used over the first 2 days (6). However, there is little guidance when choosing between commonly available crystalloid alternatives like isotonic saline (IS) and Lactated Ringer's (LR) solution.

Crystalloids can differ markedly in chloride content and strong ion difference (SID, approximated by sodium minus chloride concentrations) (7). Balanced fluids, like LR, have an electrolyte composition close to plasma (higher SID and physiologic chloride content) but are not commonly used during sepsis. In contrast, solutions such as IS, with a SID = 0, are not balanced but are used routinely for resuscitation during sepsis. IS has a supraphysiologic chloride content and is the typical "control" fluid in large randomized clinical trials (8, 9). Till recently, studies have largely focused on contrasting crystalloids against colloids rather than comparing the different crystalloids (8–10). Resuscitation with IS induces hyperchloremia and metabolic acidosis (11–14) which has been associated with undesirable consequences in preclinical (15, 16), human volunteer (17), and recent observational studies (18–20), especially alterations in renal blood flow (15–17, 20, 21). There is also evidence of potentially important effects on immune function (22–24). Balanced fluids avoid these biochemical effects (14, 21) and have been associated with reduced perioperative mortality (18, 19) and ICU morbidity (20). Accordingly, there may be reason to believe that crystalloid choice affects outcomes in sepsis, and we examined the association between receipt of balanced fluids (vs not) during initial resuscitation and in-hospital mortality, renal morbidity, ICU, and hospital lengths of stay (LOS) in a large cohort of adults admitted with vasopressor-dependent sepsis.

MATERIALS AND METHODS

Setting and Subjects

We conducted a retrospective cohort study of patients admitted to one of at least 360 geographically and structurally diverse hospitals in the United States that were members of the Premier healthcare alliance (Premier, Charlotte, NC) between November 2005 and December 2010. In addition to information from standard hospital discharge files, Premier maintains detailed billing databases with itemized, date-stamped logs of all patient charges accruing daily and prospectively including medications, fluids, diagnostic tests, and therapeutic services used during hospitalization (billable line items).

Patients were included in our analysis if they were inpatients 18 years old or older, with a principal or secondary diagnosis of sepsis (*International Classification of Diseases, Ninth Edition, Clinical Modification* [ICD-9-CM] codes: 038, 020.0, 790.7, 117.9, 112.5, 112.81, or 995.92, as described by Martin et al [25]) and a known in-hospital mortality outcome. To increase the likelihood that patients were critically ill and being treated for sepsis, we restricted inclusion to patients who were in an ICU receiving vasopressors by day 2 and had blood cultures and three consecutive days of treatment with antibiotics (initiated within the first two hospital days). We excluded all patients who underwent any surgery (based on All Patient Refined-Diagnosis-Related Group codes) ensuring a relatively homogeneous "medical" population. Further, for inclusion in the study, we required that patients receive at least 2 L of crystalloids by day 2 (i.e., resuscitation rather than maintenance therapy). Patients that were transferred (interfacility) were excluded as prior treatments or outcomes were unknown. A study exemption letter was obtained from the Baystate Medical Center Institutional Review Board.

Choice and Volume of IV Fluids

Exposure was defined based on the type and amount of crystalloids received during the initial resuscitation period, that is, on hospital days 1 and 2 (day 1 is often a fractional day). All patients in the "no-balanced fluid" group received only crystalloids with a SID = 0 such as IS with or without 5% dextrose. In contrast, patients in the "balanced fluids" group received varying amounts of both balanced (such as LR) and nonbalanced solutions (mainly IS), and we categorized these patients based on the proportion of balanced fluids received (calculated as the total balanced fluid volume divided by the total crystalloid volume over the first 2 days). Very few patients (< 1%) received exclusively balanced fluids. Dose-response relationships were analyzed according to proportion of balanced fluids received. For example, mortality was compared across patients receiving less than 20%, 20–40%, 40–60%, 60–80%, and 80–100% of total fluids as balanced solutions. We accounted for all fluid exposures regardless of initial patient location (prior to ICU admission). Total volumes were calculated based on cumulative charges for 500 and 1,000 mL units (IV bags). Smaller volumes, likely representing carrier solutions, were excluded from totals. We also excluded patients with missing or invalid fluid charges.

Patient, Hospital, and Cotreatment Information

Patient demographics, smoking status, and 27 Elixhauser comorbidities were recorded using software provided by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality. In addition, we controlled for differences in severity of illness and patient management by accounting for the use of common diagnostic tests (e.g., echocardiography), monitoring procedures (arterial, central

venous, and Foley catheters), supportive therapies (mechanical ventilation, dialysis, blood transfusions etc), and pharmacologic treatments (e.g., steroids, diuretics, and β-blockers). Furthermore, we accounted for differences in the type and amount of colloids and the total amount of crystalloids received (26). We included individual hospitals as random effects in statistical models to adjust for the potential confounding influence of hospital-specific factors that may be associated with treatment (practice variation) and outcomes.

Outcomes

The primary outcome was in-hospital (inpatient) mortality occurring after hospital day 2. In these main analyses, we excluded very early adverse outcomes (on or before hospital day 2) to minimize the possibility of an inverse association where fluid choice might be dictated by very early outcomes (e.g., saline may be chosen for patients with acute renal failure [ARF], i.e., reverse temporality). However, as the sickest patients often receive large volumes of crystalloids and may die or require dialysis prior to day 2, we also conducted secondary sensitivity analyses including these earlier outcomes (occurring on day 2). Results were examined for consistency with the primary analysis. Postdischarge data were not available.

Secondary outcomes, based on the specific populations at risk, were ARF with and without dialysis and hospital and ICU LOS among survivors. When comparing ARF outcomes, we excluded patients with end-stage renal disease already undergoing dialysis (ICD-9-CM 585.6). ARF was defined by a code (ICD-9-CM 584.x) that was absent-on-admission (i.e., "present-on-admission" status was negative). ARF with dialysis was defined either by a procedure charge for a dialysis catheter (38.95) with a charge for dialysis (39.95) or by charge codes for dialysis supplies (Premier supply item codes) in the presence of a diagnosis of ARF (ICD-9-CM 584.x). Differences in ICU and hospital LOS were compared only among survivors.

Statistical Analyses

All analyses were performed using Stata/SE (software version 11.2; StataCorp LP, College Station, TX). We analyzed the primary exposure (data on crystalloid type and amount) for patterns and predictors of "missing-ness." Cohorts were assembled by application of inclusion/exclusion criteria. We constructed summary statistics using frequencies and proportions for categorical data and medians and interquartile range for continuous variables. Univariate comparisons were performed using chi-square or *t* tests. Using all available demographic, Elixhauser comorbidity, and cotreatment information, we constructed a multilevel mixed-effects logistic regression model to predict the propensity for receipt of balanced fluids by day 2. This model also accounts for clustering of treatments at the individual hospital level and performed significantly better than a standard logistic regression approach (shown by the increase in the c-statistic from 0.65 to 0.82; 95% CI, 0.81, 0.83) (4). Utilizing a 5:1 greedy match algorithm, we implemented 1:1 propensity score matching to adjust for baseline differences between the groups. Next, this approach was repeated to match patients within strata according to the proportion of balanced fluids received as defined above (27). The matched cohorts were evaluated for balance on all measured covariates (28). For the mortality outcome, the two groups being compared were also evenly matched on the baseline prevalence of ARF. Finally, we implemented revised propensity models when comparing new cohorts-at-risk for the ARF with and without dialysis outcomes. We took the matched nature of the data into account when deriving *p* values and 95% CIs.

In-hospital mortality and all secondary outcomes were compared in the respective propensity-matched cohorts. The association between receipt of increasing balanced fluid proportions and in-hospital mortality was estimated in the matched cohort (marginal effects of treatment) and in the entire sample (average treatment effects) (29). We also examined the "balanced fluid-mortality" relationship across quintiles of total crystalloid volume. As the mortality dose-response trend was generally linear, we did not use restricted cubic splines for estimation of incremental effects. In sensitivity analyses, we analyzed the incremental effects of receipt of balanced fluids on all outcomes within propensity-matched quintiles of total crystalloid volume and predicted mortality risk using Generalized Estimating Equation models. We explored the potential influence of a hypothetical unmeasured confounder in additional sensitivity analyses using the methods described by Lin et al (30). Given the range of known confounders in this study, we varied the magnitude of effect of the hypothetical unmeasured confounder from 1.1 to 2.0 and differences in prevalence from 10% to 40%, respectively. This identified the extent of unmeasured confounding that would be needed to negate observed effects on mortality.

RESULTS

An initial cohort of 53,448 critically ill adults was assembled for primary analysis (**Fig. 1**). Patients with missing fluid exposure data were excluded (as the ability to predict "missing-ness" was relatively limited). Most patients (87%) meeting the strict inclusion criteria were cared for in one of 190 hospitals that treated at least 100 patients with septic shock during the study period. Baseline differences between the balanced and no-balanced fluid groups, in all patient and hospital characteristics, were noted (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). The predominant crystalloid types were LR in the balanced fluid group and IS in the no-balanced fluid group (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). The median total crystalloid volume during resuscitation varied ranging from 2.5 to 10.5 L (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). We identified 3,396 patients (6.4% of the initial cohort) that received balanced fluids over the first two hospital days. Proportions of balanced fluids received varied and a majority received less than 40% of all fluids as balanced solutions (**eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). Prior to matching, compared with those resuscitated with nonbalanced fluids, patients who received balanced fluids were younger (median

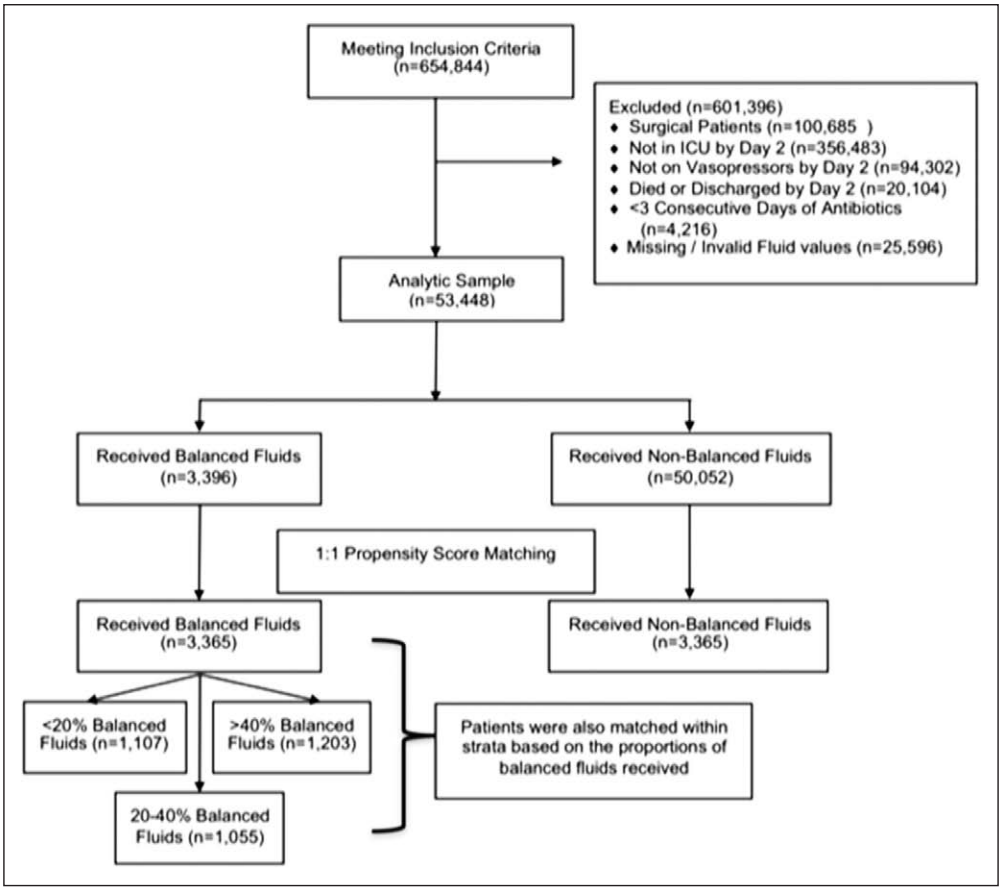

Figure 1. Creation of the study cohort by application of inclusion and exclusion criteria. Attrition was significant due to the rigorous study entry requirements. The final analytic sample (of 53,448 patients) included a relatively homogeneous group of "medical" (nonoperative) patients with sepsis in an ICU and receiving vasopressors by hospital day 2. Propensity score matching created comparable groups of patients and matching within strata of balanced fluid proportions ensured equivalence on measured characteristics.

64 vs 68 yr); received larger crystalloid volumes (median 7 vs 5 L); and were more likely to receive colloids (24% vs 19%), steroids (28% vs 23%), invasive monitoring (60% vs 52%), and mechanical ventilation (43% vs 40%), but they were less likely to have a diagnosis of heart (24% vs 33%) or chronic renal failure (20% vs 28%) and hypertension (16% vs 22%) or diabetes (6% vs 8%) with complications. Unadjusted in-hospital mortality was lower but ARF rates, dialysis, ICU, and hospital

TABLE 1. Association Between Resuscitation With Balanced Fluids and Primary and Secondary Outcomes in Propensity-Matched Cohorts

Outcome	Balanced Fluid–Matched Cohort	No-Balanced Fluid–Matched Cohort	Effect Estimate	95% CI
Absolute in-hospital mortality	19.6% (659 of 3,365)	22.8% (768 of 3,365)	Relative risk, 0.86	0.78, 0.94; $p = 0.001$
ARF with dialysis	4.52% (142 of 3,144)	4.74% (149 of 3,144)	Relative risk, 0.953	0.761, 1.194
ARF without dialysis	7.12% (159 of 2,655)	7.50% (199 of 2,655)	Relative risk, 0.950	0.784, 1.150
Hospital LOS in days (survivors)	11.26	11.37	Absolute difference, −0.11	−0.55, 0.34
ICU LOS in days (survivors)	5.39	5.50	Absolute difference, −0.11	−0.37, 0.15

ARF = acute renal failure, LOS = lengths of stay.

Analyses compare patients initially treated with balanced fluids with patients not treated with any balanced fluids and estimate effects on all outcomes (occurring beyond day 2). Relative risks for in-hospital mortality ($p = 0.001$), ARF (with and without dialysis), and absolute differences in ICU and hospital LOS among survivors are reported. ICU LOS was significantly lower in sensitivity analyses (including outcomes occurring on and beyond day 2), whereas other results remained consistent (eTable 7, Supplemental Digital Content 1, http://links.lww.com/CCM/A929).

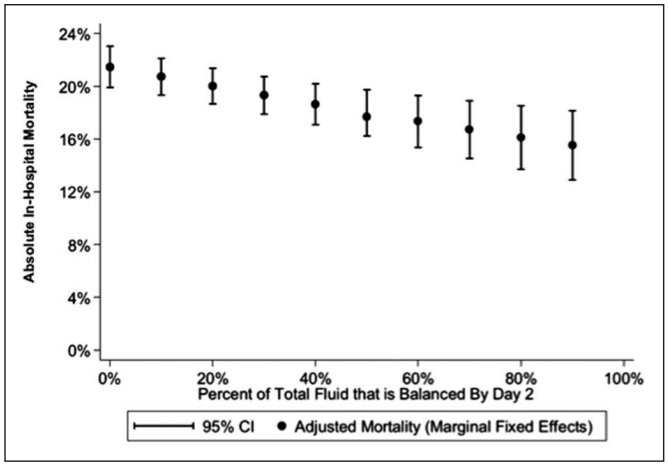

Figure 2. The *x*-axis categorizes patients based on the proportion of balanced fluids received, whereas the *y*-axis displays the adjusted absolute in-hospital mortality rate. The absolute mortality rate was lower with each increment in the proportion of balanced fluids received after accounting for all differences in demographics, comorbidities, and cotreatments. Patients receiving greater balanced fluid proportions were observed to have lower in-hospital mortality. CIs increased as fewer patients received large proportions of balanced fluids.

LOS for survivors were similar (eTable 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A929).

Propensity-Matched Analysis

Demographics, Elixhauser comorbidities, and cotreatment characteristics were equivalent after matching. We successfully matched 3,365 patients that received balanced fluids (based on the proportions received) in a 1:1 ratio with patients that did not receive any balanced fluids. Among these 6,730 patients, absolute in-hospital mortality beyond day 2 was 19.6% in the balanced fluids cohort compared with 22.8% in the no-balanced fluids cohort, a relative risk ratio of 0.86 (95% CI, 0.78–0.94) (**Table 1**). If this association represents a causal relationship, we estimate one less in-hospital death for every 31 patients treated with balanced fluids rather than saline during initial resuscitation in sepsis (95% CI, 19, 78 patients). There were no clinically significant differences in the rates of ARF with and without dialysis or in-hospital and ICU LOS beyond day 2 (Table 1). Secondary sensitivity analyses including earlier outcomes found similar results (**eTable 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929) and also showed a modest decrease in the ICU LOS among patients receiving balanced fluids (0.43 d; 95% CI, –0.75, –0.1).

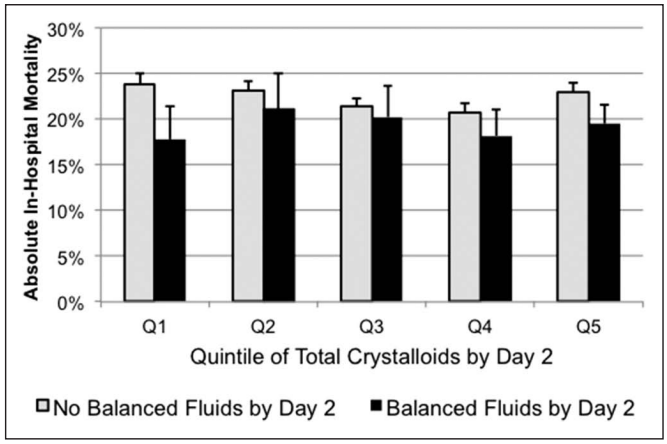

Figure 3. The *x*-axis categorizes patients based on quintiles of the total fluid volume received (median total volume in Q1 = 2.5 L, Q2 = 4 L, Q3 = 5.5 L, Q4 = 7 L, and Q5 = 10.5 L). The *y*-axis shows the adjusted in-hospital mortality. Patients receiving balanced fluids had a lower absolute mortality rate regardless of the total amount of fluid received. Patients receiving balanced fluids have lower mortalities, with significant differences within the lowest and highest quintiles.

Dose-Response and Stratified Analysis

In the cohort that was also matched within strata (according to balanced fluid proportions), the relative risk of in-hospital mortality was incrementally lower by 3.4% on average per 10% increase in the proportion of balanced fluids received (**Fig. 2**). Risk of mortality was lowest among those receiving the greatest proportion of balanced fluids regardless of the total crystalloid volume (**Fig. 3**). Mortality differences were most significant at the lowest and highest volume quintiles. Furthermore, those receiving larger proportions of balanced fluids were less likely to die within any given volume quintile (**eTable 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). For example, among patients receiving a median volume of 10.5 L, the mortality odds decreased by about 5% on average per 10% increase in the balanced fluid proportion (eTable 6, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). In addition, mortality odds decreased by 7.5% on average per 10% increase in the proportion of balanced fluids received among those at the lowest risk of death (**eTable 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). There was no significant dose-response heterogeneity for ARF, ICU, and hospital LOS outcomes (eTables 5 and 6, Supplemental Digital Content 1, http://links.lww.com/CCM/A929).

Potential for Unmeasured Confounding

An unmeasured confounder with a relative mortality risk of at least 1.5 and a difference in prevalence between groups of at least 20% would be needed for the observed mortality effects to be nullified (**eTable 7**, Supplemental Digital Content 1, http://links.lww.com/CCM/A929). We did not observe this level of confounding for any measured characteristic in our study. The largest absolute difference in prevalence of an actual comorbidity was 9% (congestive heart failure before matching), and when relative risks were higher (1.9 for metastatic cancer and 2.1 for mechanical ventilation), differences in prevalence between propensity-matched groups were minimal.

DISCUSSION

In this large observational study of critically ill adults with vasopressor-dependent sepsis, we found that the receipt of balanced fluids during initial resuscitation was associated with a lower risk of in-hospital mortality. Patients receiving the greatest proportions of balanced fluids had the lowest risk of in-hospital mortality, and dose-response effects were independent

of fluid volumes used. Marginal mortality benefits seen in the matched cohort were consistent with average beneficial effects seen in the entire sample suggesting that benefits may be generalizable across populations. We found no significant differences in the risks of ARF (with and without dialysis), and ICU and hospital LOS were similar between balanced fluids and no-balanced fluids groups.

These associations between resuscitation with balanced fluids and lower in-hospital mortality (including dose-response findings) have not been previously reported among patients with sepsis but are consistent with recent perioperative observations (19). Randomized trials have not compared the effects of different crystalloids among patients with severe sepsis (31) and none have been adequately powered to study mortality (8–10). Unlike previous studies, we did not find differences in ARF outcomes (18–20). Potential explanations may include the following: first, this large administrative dataset may be sensitive for the detection of modest yet significant differences in in-hospital mortality (an unambiguous outcome) but may be insensitive for the detection of ARF. We only included ARF as an outcome when it was absent-on-admission (making the definition specific) and prevalence was disproportionately lower than expected (~4.5% with dialysis and ~7% without dialysis) given that the prevalence of in-hospital mortality after day 2 was ~20% (4, 5). In contrast, a recent large randomized control trial among patients with severe sepsis receiving balanced fluids found that the prevalence of dialysis was 16% at 90 days with about 35% of patients doubling serum creatinine over that time frame (10). ARF rates were also much higher in a similar observational ICU study (20). Hence, we may be seeing only the tip of an ARF "iceberg" (32, 33). Second, clinician underreporting of kidney injury is well recognized with notable discordance between actual changes in serum creatinine and its corresponding recognition and documentation, that is, a large number of patients with ARF may not be coded as such (32, 33) while this is unlikely for mortality or LOS. Third, exposure groups in this study may not differ sufficiently as most patients did not receive exclusively one fluid type. The contrast in chloride load may not be large enough for substantial differences in ARF (19). However, as several studies among ICU patients have demonstrated, important mortality differences can still occur with even "minor" degrees of reduction in kidney function (32–34). Patients in our study may be especially vulnerable, as there is a strong linear relationship between the progression of kidney injury during sepsis and mortality (35, 36). Finally, it is possible that effects on systemic inflammation and immune function may influence outcomes (22, 24). As shown in a recent clinical trial among patients with acute pancreatitis, inflammatory biomarkers were significantly lower among patients that received LR compared with those that received saline (37).

Assessing the comparative effectiveness of alternative crystalloid choices is timely as guidelines do not offer specific recommendations (1). We observed a consistent association between the receipt of balanced fluids and lower mortality after rigorous control for a large number of observable confounders (including comorbidities, cotreatments, and hospital-level variation in practice). In addition, consistency of the dose-response relationship, biologic plausibility, and robustness of analyses to an unmeasured confounder suggest that there may be a modest but meaningful benefit of resuscitation with balanced fluids (38). Findings could have significant public health implications if confirmed in large RCTs as exposure to saline is currently almost universal during sepsis although balanced fluids are readily available inexpensive alternatives. Clinicians may be reluctant to use LR since it contains potassium (evidenced by lower use in chronic renal failure) (eTable 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A929) and calcium (incompatible with blood products). However, it is often underappreciated that hyperkalemia can occur with saline administration among patients with renal failure (39), and blood product compatibility is not relevant to the majority of patients as they do not receive transfusions (~80% in this cohort did not receive any RBCs). Furthermore, non-calcium-containing balanced crystalloids are available for coadministration with blood products. Therefore, the greatest barrier to use of balanced fluids may be institutional culture and a lack of awareness regarding the potential for harm associated with saline use.

Results do need to be interpreted with caution. First, the dataset is based on claims, and ascertainment of comorbidities is dependent on physician documentation and coding. However, we used an extensive list of covariates based not only on ICD-9 codes but also on daily charge files for therapies and procedures to minimize these effects. Second, this was an observational study with nonrandom treatment assignment and residual confounding is possible. We have no information about unmeasured factors that may have led to differences in fluid choice, but based on our sensitivity analysis, unmeasured confounding of considerable magnitude and direction would be necessary to alter these results. Third, we did not have physiologic or laboratory measurements, did not perform direct chart reviews, and did not have data beyond hospitalization. However, detailed information that is contained within the dataset allowed us to measure exposure carefully while adjusting for various cotreatments as proxies for severity of illness (substantially improving control for confounding). Such adjustment while incomplete is likely to be nondifferential relative to the crystalloid types (29). Finally, bias from the exclusion of missing fluid exposure data is unlikely as we were studying active comparators (rather than receipt vs nonreceipt of fluids). In addition, information on covariates was not missing in any systematic differential manner across the groups.

CONCLUSIONS

In-hospital mortality was lower following initial resuscitation with balanced versus nonbalanced crystalloids among nonoperative patients admitted with early vasopressor-dependent sepsis. Mortality was progressively lower among patients receiving greater proportions of balanced crystalloids. These findings support an urgent need for definitive clinical trials, as crystalloid therapy is nearly universal and any outcomes

differences between common alternatives could have a large public health impact.

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