Chloride Content of Fluids Used for Large-Volume Resuscitation Is Associated With Reduced Survival

Ayan Sen, MD, MS, FCCP; Christopher M. Keener, MS; Florentina E. Sileanu, MS; Emily Foldes, MS; Gilles Clermont, MD, CM, MS; Raghavan Murugan, MD, MS, FRCP, FCCM; John A. Kellum, MD, MCCM

Objective: We sought to investigate if the chloride content of fluids used in resuscitation was associated with short- and long-term outcomes.

Design: We identified patients who received large-volume fluid resuscitation, defined as greater than 60 mL/kg over a 24-hour period. Chloride load was determined for each patient based on the chloride ion concentration of the fluids they received during large-volume fluid resuscitation multiplied by the volume of fluids. We compared the development of hyperchloremic acidosis, acute kidney injury, and survival among those with higher and lower chloride loads.

Setting: University Medical Center.

Patients: Patients admitted to ICUs from 2000 to 2008.

Interventions: None.

Measurements and Main Results: Among 4,710 patients receiving large-volume fluid resuscitation, hyperchloremic acidosis was documented in 523 (11%). Crude rates of hyperchloremic acidosis, acute kidney injury, and hospital mortality all increased significantly as chloride load increased ($p < 0.001$). However, chloride load was no longer associated with hyperchloremic acidosis or acute kidney injury after controlling for total fluids, age, and baseline severity. Conversely, each 100 mEq increase in chloride load was associated with a 5.5% increase in the hazard of death even after controlling for total fluid volume, age, and severity ($p = 0.0015$) over 1 year.

Conclusions: Chloride load is associated with significant adverse effects on survival out to 1 year even after controlling for total fluid load, age, and baseline severity of illness. However, the relationship between chloride load and development of hyperchloremic acidosis or acute kidney injury is less clear, and further research is needed to elucidate the mechanisms underlying the adverse effects of chloride load on survival. (*Crit Care Med* 2016; XX:00–00)

Key Words: acute kidney injury; chloride; metabolic acidosis; saline; survival

Use of crystalloids containing supraphysiologic chloride concentrations has been associated with hyperchloremia, acidosis, and more frequent complications when compared to resuscitation with balanced crystalloids (1–6). Hyperchloremia has been shown to be independently associated with increased mortality in the ICU and postsurgical patients, and the amount of chloride received via IV infusion has been identified as an important and potentially modifiable cause of hyperchloremic acidosis (HCA) (7–9). In a prospective, sequential period study, chloride restriction was associated with a significant reduction in the occurrence of acute kidney injury (AKI) and the use of renal replacement therapy (RRT) (6). A later extended analysis of patients receiving chloride-restricted fluids showed persistent decrease of AKI and RRT rates but also found evidence of other confounders such as patient characteristics, clinician expertise, or the Hawthorne effect, which could help explain fluctuations in AKI prevalence (6, 10). However, in a cluster randomized, double-crossover trial, there was no difference in the prevalence of AKI, in-hospital mortality, or use of RRT within 90 days after enrollment in a heterogeneous population of ICU patients who received a buffered crystalloid or saline (11). The exposure to saline in this study was small (about 2 L), and patients were relatively at low risk (Acute Physiology and

All authors: Center for Critical Care Nephrology and CRISMA Center, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.

Current address for Dr. Sen: Department of Critical Care Medicine, Mayo Clinic, Scottsdale, AZ.

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For information regarding this article, E-mail: kellumja@upmc.edu

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Chronic Health Evaluation [APACHE] II, 14.1; mortality, 8%; need for RRT, 3%).

Evidence from experimental models of sepsis in animals who receive fluid resuscitation has shown that HCA induces hemodynamic instability (12) and inflammatory response (13, 14), worsens renal dysfunction (13, 14), and decreases survival (12, 14, 15). Fluid choice may therefore impact outcomes in patients requiring infusion of large volumes of IV fluids. Although studies have examined mortality in patients receiving crystalloids with different chloride concentrations, the relative contributions of chloride load and fluid volume to mortality risk remain unclear (16–19) as does the relationship between chloride load, HCA, AKI, and mortality. Furthermore, the effects of HCA on long-term outcomes are largely unknown.

MATERIALS AND METHODS

After receiving approval from the University of Pittsburgh Institutional Review Board, we interrogated the High-Density Intensive Care (HiDenIC-8) database, which contains data from all patients admitted to ICUs from 2000 to 2008 merging several computerized sources. Patient records have also been linked to national databases (National Death Index database, the Social Security Administration Death Master File, U.S. Renal Data Systems) to ascertain vital status and dialysis out to 1 year.

We defined large-volume resuscitation (LVR) as 60 mL/kg or greater in a 24-hour period and included patients receiving this volume in our analysis cohort. Patients with a history of hemodialysis or kidney transplant, a baseline creatinine greater than or equal to 4 mg/dL recorded prior to hospital admission, those with insufficient data to determine AKI status, or those who developed HCA or AKI prior to LVR or received LVR in the odds ratio (OR) were excluded. **Figure 1** outlines the selection of the study population.

We determined baseline demographic, comorbidity, and severity of illness characteristics for all patients in the LVR cohort, including derived variables, which have been described previously and include "suspected sepsis," "hypotensive index," and the Acute Physiology Score (APS)-III derived from the "acute physiology" portion of the APACHE III score (20, 21). We calculated the total chloride ion concentration of each fluid used for resuscitation in order to assess the relationship between the chloride load and amount of fluid administered during LVR. Total chloride load was determined for each patient as follows: $(C_1 . V_1) + (C_2 . V_2) + (C_3 . V_3) + (C_n . V_n)$ = chloride load (mEq), where C_n indicates chloride concentration (mEq) per liter of fluid n, and V_n is the volume of that fluid administered in the 24 hours beginning with the start of LVR. For example, if a patient received 3 L of 0.9% saline and 2 L of lactated Ringer's solution, total chloride load would be $(154 \times 3 = 462) + (109 \times 2 = 218) = 680$ mEq.

Outcomes included hyperchloremic acidosis (HCA), AKI, and mortality. HCA was determined as explained in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C147). Briefly, we defined metabolic acidosis as an arterial base deficit greater than 2 mEq/L and defined HCA as predominate etiology of metabolic acidosis after excluding other causes. AKI was determined using the widely validated Kidney Disease: Improving Global Outcomes criteria (**Table S2**, Supplemental Digital Content 2, http://links.lww.com/CCM/C148) (22). Baseline creatinine was determined as the lowest creatinine in the 1 year preceding the index hospital admission. If no baseline creatinine was available and no history of chronic kidney disease, we estimated the creatinine using the Modification of Diet in Renal Disease equation as previously described (23). We evaluated hospital mortality as well as mortality at 30 days, 90 days, and 1 year following ICU admission.

Fisher exact test and the Wilcoxon signed rank test were used for unadjusted analysis to assess the relationship between chloride load and the outcome variables. For binary outcomes, adjusted analyses were performed via logistic regression using the Hosmer-Lemeshow goodness-of-fit test for model calibration and the area under the receiver operating characteristic curve for model discrimination. Due to nonlinear relationship between chloride load and the logit of the probability for outcomes, chloride load was analyzed categorically on the basis of quartiles. Such models were adjusted for the total volume of fluid given during LVR. Alternatively, the chloride load was divided by the total volume of LVR fluids. Time-to-event outcomes were conducted in both unadjusted and adjusted analyses. For the unadjusted analyses, Kaplan-Meier plots were assessed. Adjusted analyses were performed using the Cox proportional hazards model. Where log-log plots or Shoenfeld residual plots indicated possible violation of the proportional hazards assumption, covariates were interacted with various transformations of time. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), STATA version SE 14 (StataCorp, College Station, TX), and R 3.2.2 software (https://www.r-project.org).

RESULTS

Baseline Characteristics

Of the 4,710 patients in our analysis cohort (Fig. 1), baseline characteristics and processes of care variables for patients with varying chloride loads are shown in **Table 1**. Patients who received larger chloride loads were sicker with higher APS-III scores (76.0 [55.0–101.0] for quartile 4 compared to 56.0 [40.0–76.0] for quartile 1). They were more likely to be on mechanical ventilation and vasopressors and had longer ICU stays (p values all < 0.001). There was, as expected, also a relationship between chloride load and total mean volume of fluid administered. For example, the fourth quartile of chloride load received more than twice the total volume to that of the first quartile (mean of 8 L [95% CI, 6.8–10] as compared to 3.7 L [95% CI, 3.2–4.2]).

Unadjusted Outcomes

The relationships (unadjusted) between chloride load and each of the outcomes examined are shown in **Table 2**. Crude rates of HCA, AKI, and hospital mortality all increased significantly as chloride load increased ($p < 0.001$). Importantly, the unadjusted association between chloride load and mortality

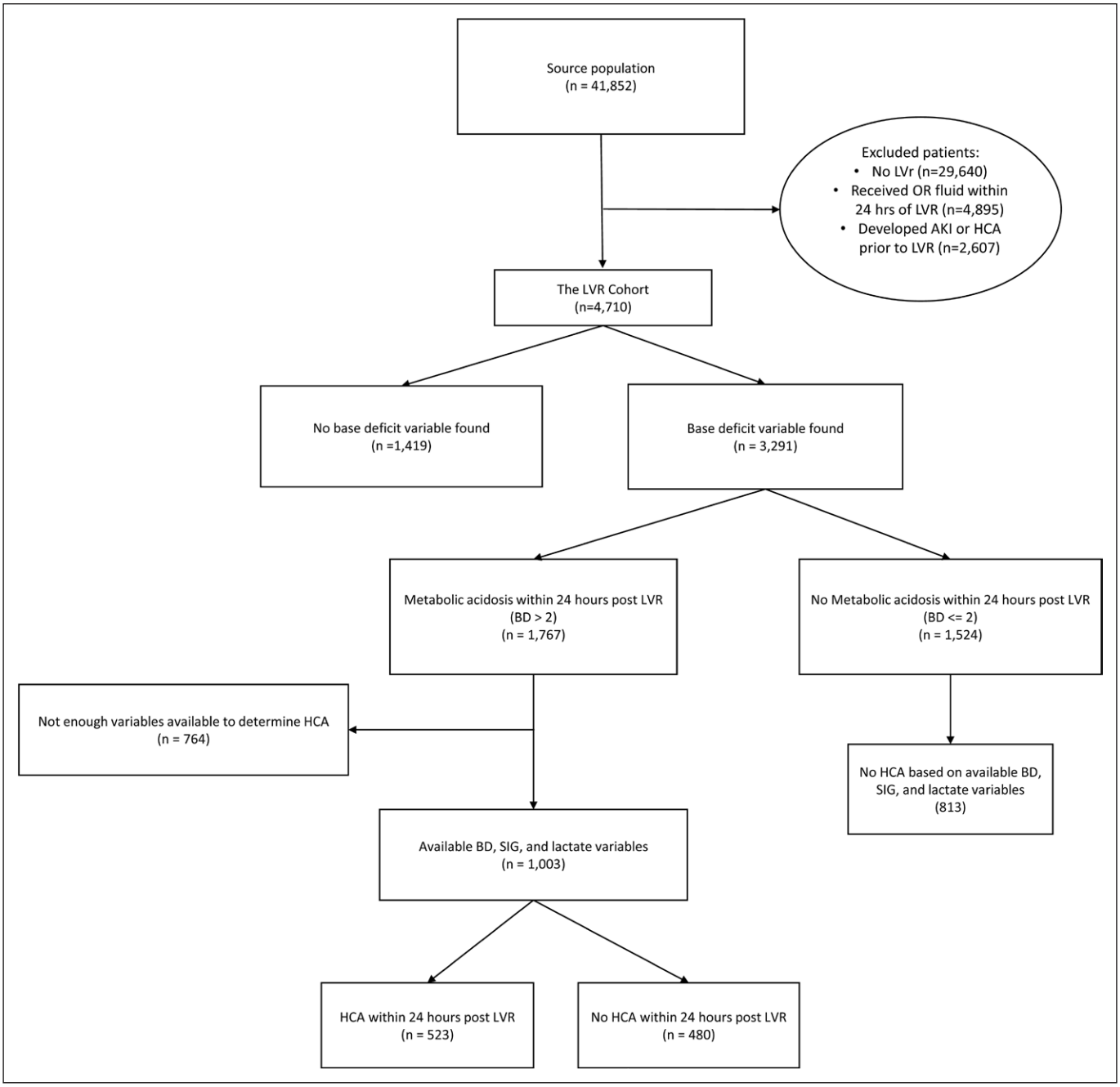

Figure 1. Study cohort selection. AKI = acute kidney injury, BD = base deficit, HCA = hyperchloremic acidosis, LVR = large-volume fluid resuscitation, OR = odds ratio, SIG = strong ion gap.

persisted out to 1 year (our maximum follow-up), where mortality for the first (lowest) quartile of chloride load was 35% but 47% for the fourth quartile ($p < 0.001$).

Chloride Load and HCA

Chloride load was strongly associated with the development of HCA in univariate analysis. However, after controlling for total fluids and APS-III, the relationship was attenuated and no longer significant across the quartiles ($p = 0.23$). Although the omnibus comparison between the models was not significant, the odds of developing HCA increased with increasing chloride load with patients in the fourth quartile having 32% higher odds of developing HCA than patients in the first quartile ($p < 0.001$) (**Table 3**, model A).

Chloride Load and AKI

Chloride load (quartiles) was associated with increasing odds of AKI even after controlling for total fluids ($p = 0.03$) (Table 3, model B). An adjusted ordinal logistic regression model yielded an OR of 1.09 ($p < 0.0001$) for a 100 mEq increase in chloride load. Adjusting for APS-III, the OR for AKI was 1.04 ($p < 0.0001$). However, when chloride load was modeled as a continuous variable, it was no longer associated with AKI once controlling for APS-III.

TABLE 1. Baseline Characteristics and Process of Care by Chloride Load ($n = 4,710$)

Characteristics mEq	Q1 (323–491)	Q2 (492–635)	Q3 (636–848)	Q4 (849–5,432)	*p*
Age, yr (%)					
18–44	316 (26.9)	287 (24.4)	249 (21.1)	300 (25.5)	< 0.001
45 to < 65	443 (37.7)	487 (41.3)	504 (42.8)	516 (43.9)	
65 to < 75	169 (14.4)	185 (15.7)	204 (17.3)	191 (16.2)	
≥ 75	248 (21.1)	219 (18.6)	221 (18.8)	169 (14.4)	
Males, *n* (%)	422 (35.9)	559 (47.5)	640 (54.3)	729 (61.9)	< 0.001
Race, *n* (%)					
White	921 (78.2)	920 (78.1)	933 (79.2)	868 (73.7)	0.05
Black	94 (8.0)	88 (7.5)	86 (7.3)	104 (8.8)	
Other	162 (13.8)	170 (14.4)	159 (13.5)	205 (17.4)	
Body mass index, median (IQR)	20.8 (18.5–23.6)	23.5 (20.8–26.1)	25.1 (22.5–28.3)	26.6 (23.0–30.8)	< 0.001
Acute Physiology Score-III[a], median (IQR)	56.0 (40.0–76.0)	62.0 (44.0–81.0)	64.0 (45.0–83.0)	76.0 (55.0–101.0)	< 0.001
Comorbid condition, *n* (%)					
Diabetes	137 (11.6)	166 (14.1)	186 (15.8)	174 (14.8)	0.028
Cardiac disease	149 (12.7)	150 (12.7)	134 (11.4)	143 (12.1)	0.73
Chronic renal disease	61 (5.2)	61 (5.2)	66 (5.6)	45 (3.8)	0.21
Vascular disease	96 (8.2)	91 (7.7)	104 (8.8)	74 (6.3)	0.13
Multiple comorbidity	605 (51.4)	586 (49.7)	552 (46.9)	516 (43.8)	0.001
Nephrotoxins[a,b], *n* (%)	560 (47.6)	545 (46.3)	558 (47.4)	538 (45.7)	0.77
Surgical admission, *n* (%)	653 (59.1)	670 (61.3)	633 (58.2)	625 (58.1)	0.40
Mechanical ventilation[a], *n* (%)	784 (66.6)	842 (71.5)	860 (73.0)	953 (81.0)	< 0.001
Serum creatinine, mg/dL, median (IQR)					
Baseline creatinine	0.8 (0.6–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.1)	0.022
Admission creatinine	0.9 (0.7–1.2)	0.9 (0.7–1.3)	1.0 (0.8–1.4)	1.1 (0.8–1.7)	< 0.001
Reference creatinine	0.8 (0.6–1.0)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.9 (0.7–1.1)	< 0.001
Hypotensive index[a,c] > 0, *n* (%)	431 (36.6)	573 (48.7)	645 (54.8)	825 (70.5)	< 0.001
Fluids in liters, median (IQR)	3.7(3.2–4.2)	4.4(3.9–5.0)	5.4(4.8–6.0)	8.0 (6.8–10.0)	< 0.001
Vasopressors[a], *n* (%)	290 (24.6)	383 (32.5)	485 (41.2)	695 (59.0)	< 0.001
Hospital length of stay, days	15.0 (9.0–26.0)	15.5 (8.0–28.0)	16.0 (8.0–27.0)	16.0 (7.0–28.0)	0.45
ICU length of stay, days	6.0 (3.0–11.0)	6.0 (4.0–14.0)	7.0 (4.0–13.0)	8.0 (4.0–16.0)	< 0.001
Sepsis[a,d], *n* (%)	180 (15.3)	222 (18.8)	284 (24.1)	382 (32.5)	< 0.001

IQR = interquartile range.

[a]Measured within 24 hr of ICU admission.

[b]Nephrotoxins include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, vancomycin, aminoglycoside, calcineurin inhibitor, nonsteroidal, and diuretics.

[c]Area under the curve for severity and duration of hypotension (details available in Materials and Methods section).

[d]"Suspected sepsis" defined as ordering of blood cultures and antibiotics (details available in Materials and Methods section).

HCA and AKI

Using ordinal logistic regression, we did find that HCA (unadjusted) was associated with AKI (OR, 1.24; $p = 0.025$). However, age and APS-III adjustment was not performed as the proportional odds assumption was no longer valid after adding these variables ($p < 0.0001$). Therefore, the association of HCA with AKI could not be ascertained after controlling for age and APS-III in multivariate analysis.

TABLE 2. Outcomes Stratified by Chloride Load

Quartile	Q1	Q2	Q3	Q4	
mEq	(323–491)	(492–635)	(636–848)	(849–5,432)	*p*
Hyperchloremic acidosis within 24 hr of large-volume fluid resuscitation, *n* (%)					
Missing	758 (64.4)	748 (63.5)	737 (62.6)	651 (55.3)	< 0.001
No	335 (28.5)	341 (28.9)	321 (27.2)	296 (25.1)	
Yes	84 (7.1)	89 (7.6)	120 (10.2)	230 (19.5)	
Maximum Kidney Disease: Improving Global Outcomes, *n* (%)					
No acute kidney injury	329 (27.9)	245 (20.8)	226 (19.2)	163 (13.9)	< 0.001
Stage 1	221 (18.8)	211 (17.9)	165 (14.0)	151 (12.8)	
Stage 2	371 (31.5)	421 (35.7)	433 (36.8)	362 (30.8)	
Stage 3	256 (21.7)	301 (25.5)	354 (30.1)	499 (42.5)	
Hospital mortality, *n* (%)	226 (19.2)	285 (24.2)	298 (25.3)	417 (35.4)	< 0.001
Mortality after ICU admission, days, *n* (%)					
30	207 (17.6)	266 (22.6)	289 (24.5)	387 (32.9)	< 0.001
90	294 (24.9)	343 (29.1)	374 (31.7)	480 (40.8)	< 0.001
365	407 (34.6)	432 (36.7)	481 (40.8)	553 (46.9)	< 0.001

Q1–Q4 = quartiles 1 through 4.

Chloride Load and Mortality

The relationship between chloride load and mortality remained consistent at the various time points assessed. At 30 days following ICU admission, the odds of mortality increased dramatically with increasing chloride load with a greater than 70% increase in the odds of mortality for a patient receiving a chloride load in the fourth quartile compared to the first quartile (Table 3, model C). This relationship persisted after controlling for the total volume of fluids and baseline severity of illness (APS-III). Similar results were observed at hospital discharge and at 90 days (**Table S3**, Supplemental Digital Content 3, http://links.lww.com/CCM/C149). The model assessing the relationship between chloride load, in quartiles, and mortality at 1 year showed good fit (Hosmer-Lemeshow p value = 0.76), and the continuous model evaluating the relationship between chloride load and total volume remained significant ($p < 0.001$). Chloride load remained significantly associated with increased mortality whether analyzed continuously or by quartiles and even after controlling for total fluids, age, and baseline severity of illness (APS-III) ($p = 0.005$; Table S3, Supplemental Digital Content 3, http://links.lww.com/CCM/C149). When compared to the first quartile, the fourth quartile of chloride load had an OR of 1.49 (1.16–1.92). A Cox proportional hazards model adjusting for total volume of fluid given, age, and APS-III revealed a hazard ratio (HR) of 1.005 ($p = 0.0015$). We also fit a separate model that included interaction terms between the model variables and time. The hazards ratios for the interaction model are summarized using a curve over time with a reference line for the HR under the proportional hazards assumption (**Fig. 2**).

DISCUSSION

Hyperchloremia has been identified in up to 80% of patients admitted to a mixed medical-surgical ICU (24). When large amounts of saline are infused, the kidney is slow to excrete the excess chloride load (25). In animal studies, sustained renal vasoconstriction was specifically related to hyperchloremia, which was potentiated by previous salt depletion and related to the tubular reabsorption of chloride (26, 27). Consistent with prior studies, we have shown increased risk for mortality and complications (AKI) with increased use of fluids containing high chloride concentrations. However, we are the first to show that chloride load is associated with a long-term mortality hazard, at least as far as 1 year. In patients receiving LVR with a chloride load above the median (i.e., third and fourth quartiles), there was decreased survival compared to the first quartile. Specifically, compared to the lowest quartile of chloride load, the highest quartile was 1.7 and 1.49 times as likely to die by 90 days and 1 year, respectively, after controlling for fluid load, age, and baseline severity. When examined as a continuous variable, each 100 mEq increase in chloride load was associated with 5.5% increase in mortality over 1 year (HR, 1.055; $p = 0.0015$) again after adjusting for volume, age, and severity of illness.

We have also shown that the relationship between chloride load and mortality is complex. We found a relationship between chloride load and AKI in univariate models, but multivariate

TABLE 3. Logistic Regression Models for Chloride Load Quartiles and Clinical Outcomes

Effect	OR	p[a]
A. Hyperchloremic acidosis ($n = 2,526$)[b]		
Chloride load Q2	0.88 (0.63–1.22)	0.23
Chloride load Q3	1.10 (0.78–1.53)	
Chloride load Q4	1.32 (0.86–2.01)	
Fluids in liters	1.15 (1.08–1.22)	< 0.0001
Age	1.00 (1.00–1.01)	0.27
APS-III	1.02 (1.02–1.03)	< 0.0001
B. Acute kidney injury ($n = 4,706$)[c]		
Chloride load Q2	1.30 (1.06–1.59)	0.03
Chloride load Q3	1.33 (1.07–1.66)	
Chloride load Q4	1.41 (1.02–1.96)	
Fluids in liters	1.04 (0.98–1.09)	0.18
Age	1.03 (1.02–1.03)	< 0.0001
APS-III	1.03 (1.02–1.03)	< 0.0001
C. Mortality by 30 d ($n = 4,708$)[d]		
Chloride load Q2	1.26 (1.02–1.56)	0.002
Chloride load Q3	1.35 (1.09–1.69)	
Chloride load Q4	1.71 (1.30–2.26)	
Fluids in liters	1.00 (0.97–1.04)	0.95
Age	1.03 (1.03–1.04)	< 0.0001
APS-III	1.02 (1.02–1.02)	< 0.0001

APS = Acute Physiology Score, OR = odds ratio.

[a]p values for effect of chloride load reflect the omnibus test across all four quartiles (comparator is always quartile 1).

[b]AUC = 0.8212, Hosmer-Lemeshow goodness-of-fit test p value=0.022.

[c]AUC = 0.7581, Hosmer-Lemeshow goodness-of-fit test p value = 0.4105.

[d]AUC = 0.7260, Hosmer-Lemeshow goodness-of fit-test p value = 0.8277.

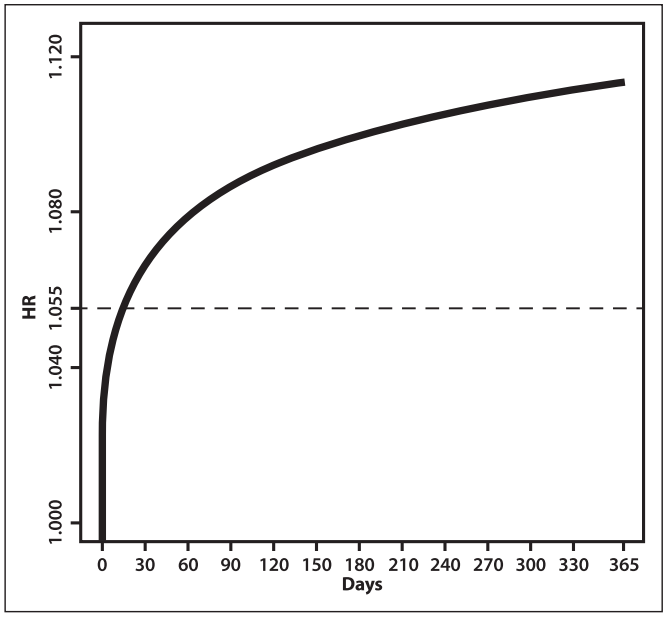

Figure 2. Hazard ratio (HR) plot. This figure displays the HR for a 100 unit increase in chloride load for a Cox proportional hazards model adjusting for total volume of fluid given, age, and Acute Physiology and Chronic Health Evaluation III (*dotted line*), as well as the HR at various days when an interaction term is incorporated to relax the proportional hazards assumption (*solid curve*) and the same set of adjusting covariates. The simple proportional hazard model has a HR of 1.055 ($p = 0.0015$). The joint significance of the main effect for chloride load and the interaction term between chloride load and log time has a p value of 0.0016.

models that included baseline severity of illness (APS-III) did not perform acceptably. Furthermore, continuous chloride load was no longer significantly associated with AKI once controlling for APS-III. Thus, AKI may not be the only, or even predominant, effect of chloride load to explain its relationship with mortality.

A similar complex relationship may exist for HCA. Importantly, the HiDenIC-8 database, which included detailed laboratory data, afforded us the opportunity to examine the contribution of HCA to clinical outcomes, whereas previous studies were unable to do so (7, 9). We hypothesized that in patients receiving LVR, higher chloride load would be associated with greater prevalence of HCA, and this is indeed what we found. However, this association was no longer significant after controlling for total fluids administered and APS-III. Admittedly, our ascertainment of HCA was not complete because clinicians only characterized acid-base variables sufficiently to determine HCA in less than 40% of patients. Nevertheless, in those patients who had their acid-base status characterized, HCA was not linked to chloride load once we controlled for other variables. Total volume was a strong predictor of HCA and is obviously a determinant of chloride load. One could argue that we should not have attempted to control for total volume in our models since greater volumes of solutions such as 0.9% saline may lead to adverse effects, whereas small volumes may be well tolerated—and it would be important to understand this relationship. However, our intent was to understand whether fluid composition, rather than volume per se, was associated with harm, and we did demonstrate such an association between chloride load and AKI and also with mortality. The fact that this relationship could not be shown with HCA is notable.

One possible explanation for our findings is that supraphysiologic chloride solutions may complicate existing disease but may be well tolerated in less severely ill patients. Although LVR patients are not healthy, by definition, patients with relatively intact renal function and acid-base balance may be able to handle the chloride load, whereas patients with underlying renal dysfunction or metabolic acidosis already at the start of LVR may not be. The use of saline has long been known to be associated with an increased risk of hyperchloremic metabolic acidosis (28), but it has only recently been shown that these metabolic changes can result in decreased renal blood flow and renal cortical hypoperfusion, as demonstrated in healthy volunteers (29). Yet, these volunteers could tolerate these effects and did not develop AKI.

Alternative explanations for the association between chloride load and mortality have been sought. For example, immunologic

effects of metabolic acidosis have been described (30, 31), as well as lung injury (32). Acidosis has been associated with lung inflammation by increase in lung myeloperoxidase activity and, thereby, increased lung injury scores in animal models (32).

A clinical trial by Yunos et al (10) demonstrated a decreased AKI prevalence and use of RRT in ICU patients with implementation of a chloride-restricted strategy. However, this study did not explore the relationship between high chloride load and development of HCA. In the 0.9% Saline vs Plasma-Lyte 148 for ICU fluid Therapy trial, a cluster randomized double-crossover trial, no difference in outcomes was seen using saline versus buffered crystalloid solution (plasmalyte) (11). However, in this study, the mean crystalloid infusion was around 2 L which is considerably lower than our starting point of LVR that included 60 mL/kg over a 24-hour period. The authors do suggest that the CIs around the point estimate of treatment effect were wide, and the possibility of a clinically significant effect of AKI was not excluded. In addition, the patients in this trial were of lower acuity than our LVR population. Higher risk patients may still benefit from avoiding chloride-rich fluids based on our results. A meta-analysis of 21 studies that included randomized clinical trials and observational studies found a significantly higher risk of AKI (relative risk [RR], 1.64; 95% CI, 1.27–2.13; $p < 0.001$) and hyperchloremia/metabolic acidosis (RR, 2.87; 95% CI, 1.95–4.21; $p < 0.001$) but no mortality effect (33).

Our study has important strengths. Most importantly, our ascertainment of exposure (chloride load) and clinical outcomes including HCA and AKI is based on primary data (documented infusion of fluid, laboratory volumes, and urine volume) not on billing or other administrative codes. We carefully determined fluid composition and characterized acid-base disorders (rather than relying only on hyperchloremia) to a level of detail not performed (to our knowledge) in any previous study on this topic. Similarly, we ascertained AKI using changes in both creatinine and urine output using the latest international guidelines (22). We have previously shown that failure to include urine output criteria significantly underestimates AKI (34). Finally, we were able to link our data with national databases to determine long-term hazards.

Our study also has important limitations. We did not include patients receiving LVR in the OR since we could not ascertain fluid administration to the same level of detail nor could we adequately account for blood loss. In nearly two thirds of patients receiving LVR, we could not determine if HCA occurred because clinicians did not characterize their acid-base status. We focused on patients receiving at least 60 mL/kg in a 24-hour period because this is where we would anticipate the most effects of chloride load given a large exposure and a susceptible population. However, it is possible that some effect might be observed with smaller volumes in less critically ill patients. Our results cannot address this question nor can we state what the minimal exposure to supraphysiologic chloride solutions would be in order to observe any hazard. Our methods do not address what the optimal alternative fluid to saline would be. Our patients received a variety of alternative fluids and we did not attempt to analyze differences among these fluids (**Table S4**, Supplemental Digital Content 4, http://links.lww.com/CCM/C150). Our database is now roughly 10–15 years old, and practice has changed in this time. However, we note that fluid resuscitation has been relatively unchanged, at least in North America, where saline remains the preferred fluid. Finally, because this was not a randomized trial, we cannot entirely control for bias. Patients with higher illness severity received more fluids and thus more chloride. However, the mortality signal remained after controlling for both baseline severity (APS-III) and total fluid volume.

CONCLUSIONS

Among patients receiving LVR (> 60 mL/kg over a 24 hr), increasing chloride load is associated with significant adverse effects on survival out to 1 year even after controlling for total fluid administered and baseline severity of illness. These results add to a growing body of literature, suggesting that large volumes of high chloride solutions may be deleterious. However, the mechanisms responsible for these effects remain unclear. We recommend avoiding supraphysiologic chloride solutions when resuscitation volumes are likely to exceed 60 mL/kg.

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