Intensive Care Med (2014) 40:1897–1905
DOI 10.1007/s00134-014-3505-3

ORIGINAL

Andrew D. Shaw
Karthik Raghunathan
Fred W. Peyerl
Sibyl H. Munson
Scott M. Paluszkiewicz
Carol R. Schermer

Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS

Received: 13 May 2014
Accepted: 20 September 2014
Published online: 8 October 2014

Take-home message: A retrospective analysis of US electronic health record (EHR) data revealed that in patients meeting systemic inflammatory response syndrome (SIRS) criteria, greater chloride loads received during crystalloid resuscitation were associated with greater in-hospital mortality, an effect that was found to be independent of fluid volume administered. These data support existing evidence that crystalloids with lower chloride content may be preferable for use in patients with SIRS.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-014-3505-3) contains supplementary material, which is available to authorized users.

A. D. Shaw (✉)
Division of Cardiothoracic Anesthesiology, Department of Anesthesiology, Vanderbilt University Medical Center, 1215 21st Avenue S., Suite 5160 MCE NT, Office 5163, Campus Box 8274, Nashville, TN 37232-8274, USA
e-mail: andrew.shaw@vanderbilt.edu
Tel.: 615-322-4650

K. Raghunathan
Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA

K. Raghunathan
Anesthesiology Service, Durham VA Medical Center, Durham, NC, USA

F. W. Peyerl · S. H. Munson · S. M. Paluszkiewicz
Boston Strategic Partners, Inc., Boston, MA, USA

C. R. Schermer
Baxter Healthcare Corporation, Deerfield, IL, USA

Abstract *Purpose:* Recent data suggest that both elevated serum chloride levels and volume overload may be harmful during fluid resuscitation. The purpose of this study was to examine the relationship between the intravenous chloride load and in-hospital mortality among patients with systemic inflammatory response syndrome (SIRS), with and without adjustment for the crystalloid volume administered. *Methods:* We conducted a retrospective analysis of 109,836 patients ≥18 years old that met criteria for SIRS and received fluid resuscitation with crystalloids. We examined the association between changes in serum chloride concentration, the administered chloride load and fluid volume, and the 'volume-adjusted chloride load' and in-hospital mortality. *Results:* In general, increases in the serum chloride concentration were associated with increased mortality. Mortality was lowest (3.7 %) among patients with minimal increases in serum chloride concentration (0–10 mmol/L) and when the total administered chloride load was low (3.5 % among patients receiving 100–200 mmol; $P < 0.05$ versus patients receiving ≥500 mmol). After controlling for crystalloid fluid volume, mortality was lowest (2.6 %) when the volume-adjusted chloride load was 105–115 mmol/L. With adjustment for severity of illness, the odds of mortality increased (1.094, 95 % CI 1.062, 1.127) with increasing volume-adjusted chloride load (≥105 mmol/L). *Conclusions:* Among patients with SIRS, a fluid resuscitation strategy employing lower chloride loads was associated with lower in-hospital mortality. This association was independent of the total fluid volume administered and remained significant after adjustment for severity of illness, supporting the hypothesis that crystalloids with lower chloride content may be preferable for managing patients with SIRS.

Keywords Fluid therapy · Balanced solutions · Resuscitation · Crystalloid · Chloride

Introduction

Large volumes of intravenous (IV) crystalloids are frequently given for the purpose of resuscitating critically ill or postoperative patients [1]. While there is general agreement regarding the benefits of fluid resuscitation, there is significant variation in the type and amount of fluid used, and the debate regarding the ideal resuscitation fluid is ongoing [2]. Crystalloids most commonly used for resuscitation are 0.9 % "normal" saline, which contains supra-physiologic levels of sodium and chloride (154 mmol/L), and "balanced" crystalloids such as Ringer's lactate, Hartmann's, Ringer's acetate or Plasma-Lyte® (Baxter Healthcare, Deerfield, IL, USA), which typically have more physiological electrolyte concentrations (98–112 mmol/L chloride; 130–140 mmol/L sodium) [1].

Recent guidelines recommend the use of balanced crystalloids for fluid resuscitation; however, these guidelines have been scrutinized because of a lack of supportive evidence from prospective randomized trials [3, 4]. When compared to balanced crystalloids, 0.9 % saline has been extensively studied in large randomized trials in critically ill patients and remains widely used [5–7]. Infusion of 0.9 % saline induces hyperchloraemia and metabolic acidosis in healthy individuals and surgical patients [8–13]. Similarly, resuscitation of critically ill patients with crystalloids containing supra-physiologic chloride concentrations has been associated with higher rates of hyperchloraemia, metabolic acidosis and clinical complications versus resuscitation with balanced crystalloids [14–19].

Recent studies indicate that elevated serum chloride is associated with serious clinical consequences in certain inpatient populations. Hyperchloraemia has been shown to be independently associated with increased mortality in intensive care unit (ICU) and postsurgical patients, and the amount of chloride received via IV infusion has been identified as an important and potentially modifiable cause of hyperchloraemic acidosis [20, 21]. Fluid choice may therefore impact outcomes in patients requiring infusion of large IV fluid volumes.

While studies have examined mortality in patients receiving crystalloids with different chloride concentrations [11, 16, 22–25], the relative contributions of chloride load and fluid volume to mortality risk remain unclear. The current study examined data from a large US electronic health record (EHR) database. We investigated the association between chloride load and in-hospital mortality among patients meeting systemic inflammatory response syndrome (SIRS) criteria who received IV crystalloids, with and without adjustment for the total fluid volume administered. SIRS patients represent an important population, given that they are frequently administered large volumes of chloride-containing fluids, as well as the known associations between hyperchloraemia and adverse outcomes in surgical and critically ill patients.

Methods

Design and patients

This study retrospectively analysed prospectively collected US inpatient data between 1 January 2009 and 31 March 2013, sourced from the HealthFacts® (Cerner Corp., Kansas City, MO) EHR database and was approved by the Duke University IRB. Inclusion criteria (Supplementary Fig. 1) were prospectively defined to identify hypovolaemic patients requiring fluid resuscitation, and included age $\geq$18 years; presence of SIRS criteria (tachycardia [HR $>$ 90 bpm] plus any of the following: (1) temperature $>$38 or $<$36 °C; (2) $\geq$20 breaths/min or $PaCO_2 \leq 32$ mmHg; (3) leukocytes $\geq$12,000 or $\leq$4,000 cells/mm^3); receipt of $>$500 mL crystalloid resuscitation solution within 2 days of SIRS qualification ($\geq$2 administrations $>$250 mL); and hospitalization $\geq$24 h. Tachycardia was required for inclusion because it is readily captured in the database and can be used as a clinical marker for hypovolaemia [26]. Crystalloid resuscitation solutions included 0.9 % saline, Ringer's lactate and other balanced crystalloids. Dextrose-containing solutions (e.g. 5 % dextrose in water) were also included in total fluid volume, but were considered maintenance fluids and did not count toward resuscitation volume inclusion requirements. Patients receiving any fluid containing hydroxyl-ethyl starch or albumin, plasma protein fraction (PPF), hypertonic saline or 0.45 % saline, or receiving $>$1 L total fluid on the day preceding SIRS qualification were excluded. Gelatins (Gelofusine®, Haemaccel®) are unavailable in the USA, and were not specified as exclusion criteria. Patients undergoing cardiac procedures (Supplementary Table 1) were excluded, as were patients with end-stage renal disease (ESRD; ICD-9 585.6), since large-volume resuscitation is infrequently used for patients with ESRD.

Data source

HealthFacts® is a de-identified, Health Insurance Portability and Accountability Act (HIPAA)-compliant, US EHR database covering 486 clinical facilities and hospital systems. The study dataset was extracted from the database such that duplicates and entries with missing/incomplete data were removed. Care was taken to avoid multiple counts of patient encounters, such that the dataset represents individual patients.

Analysis and statistics

Patient demographics and surgical procedures undergone prior to SIRS qualification and coded as primary or secondary were collected (Table 1). Primary discharge diagnoses (final, billing, discharge), the most well-populated diagnosis fields in the database, are reported. Elixhauser comorbidities were identified using Agency for Healthcare Research and Quality (ARHQ) criteria and comorbidity scores were calculated according to published methodology [27, 28]. Baseline and peak chloride concentrations were defined as the lowest concentration on the day of SIRS qualification and highest concentration within 72 h following SIRS qualification, respectively. Change in concentration was defined as the difference between baseline and peak values.

Table 1 Summary of patient characteristics

Patient characteristic	All patients (n = 109,836)
Age	
Mean (SD)	58.9 (18.8)
Median (range)	60 (18–90)
18−50 years, *n* (%)	35,635 (32.4)
51–64 years, *n* (%)	28,673 (26.1)
≥65 years, *n* (%)	45,528 (41.5)
Gender[a]	
Female, *n* (%)	60,124 (54.7)
Male, *n* (%)	49,658 (45.2)
Race	
White, *n* (%)	71,880 (65.4)
Black, *n* (%)	29,143 (26.5)
Hispanic, *n* (%)	1,911 (1.7)
Asian/Pacific, *n* (%)	1,325 (1.2)
Other, *n* (%)	4,250 (3.9)
Not specified, *n* (%)	1,327 (1.2)
Most common primary discharge diagnoses[b,c]	
Pneumonia, *n* (%)	10,075 (9.2)
Septicaemia, *n* (%)	7,454 (6.8)
General symptoms, *n* (%)	7,295 (6.6)
Symptoms involving respiratory system and other chest symptoms, *n* (%)	6,962 (6.3)
Other symptoms involving abdomen and pelvis, *n* (%)	5,600 (5.1)
Patients undergoing surgical procedure prior to SIRS qualification, *n* (%)[d]	1,562 (1.4)
APS	
Mean (SD)	7 (6)
Median (range)	6 (0–45)
Elixhauser comorbidity score	
Mean (SD)	4 (7)
Median (range)	3 (−18 to 54)

APS acute physiology score

[a] Gender not specified for 54 patients

[b] Primary discharge diagnoses present in ≥5 % of patients (primary discharge diagnosis reported in database for 94.7 % of study population)

[c] Pneumonia includes pneumonia organism unspecified, bacterial pneumonia organism unspecified, viral pneumonia organism unspecified; septicaemia includes unspecified septicaemia, septicaemia due to Gram-negative organism, streptococcal septicaemia; general symptoms include generalized pain, malaise and fatigue, altered mental status; symptoms involving respiratory system and other chest symptoms include shortness of breath, chest pain; other symptoms involving abdomen and pelvis include abdominal pain, swelling, ascites

[d] Most common surgical procedures: total knee replacement (n = 126), open reduction of fracture of femur with internal fixation (n = 57), closure of skin and subcutaneous tissue (other sites) (n = 54), temporary tracheostomy (n = 50), other lysis of peritoneal adhesions (n = 43) and total hip replacement (n = 43)

Total IV fluid volumes and chloride/sodium loads were examined for the day preceding SIRS qualification for inclusion/exclusion, and from the day of SIRS qualification plus 3 days (72 h) for outcome analysis. Total volumes were determined by summing volumes for all resuscitation and maintenance solutions with product size >250 mL, in order to avoid volumes commonly used for drug delivery/admixture. Volumes were determined by (1) the EHR "order volume" field, or (2) label bag volume for the National Drug Code (NDC) for the order. Total chloride load was calculated by summing the chloride content for all solutions >250 mL. Chloride load was adjusted for fluid volume received by dividing total mmol chloride by total fluid volume. We refer to this measure, expressed in mmol/L, as the "volume-adjusted chloride load." "Volume-adjusted sodium load" was determined using the same methodology.

Patients were prospectively grouped in 10 mmol/L increments for analysis of serum chloride concentration and volume-adjusted chloride or sodium load, 100 mmol increments for analysis of chloride load, and 1,000 mL increments for analysis of fluid volume. Mortality was determined by the database discharge value of "deceased," and rates were compared between groups using a two-proportion z test. To control for multiple comparisons, a Bonferroni correction was applied to calculated P values by multiplying by the number of pairwise comparisons. A P value <0.05 was used to define statistical significance. Regression functions and 95 % confidence intervals were weighted on the basis of the number of patients in each group, and appropriateness of fit was assessed using the coefficient of determination (R^2) and P value of the regression model.

Mortality odds ratios (ORs) associated with volume-adjusted chloride load were calculated with and without adjustment for severity of illness using the acute physiology score (APS) [29]. ORs represent mortality odds associated with a 10 mmol/L incremental increase in volume-adjusted chloride load (for data points <105 and ≥105 mmol/L). Post hoc analysis examined ORs associated with a 1 mmol/L incremental increase in volume-adjusted chloride load for data below, within, and above the 98–110 mmol/L range, which is the normal serum chloride range reported by hospitals in the database.

Results

Patients

Overall, 109,836 patients from 124 hospitals were included in the analysis based on the defined inclusion criteria. Mean age was 58.9 ± 18.8 years. In total, 41.5 % ($n = 45{,}528$) of patients were ≥65 years old and 54.7 % ($n = 60{,}124$) were female (Table 1). The most common primary discharge diagnoses were pneumonia, septicaemia, general symptoms, symptoms involving respiratory system and other chest symptoms, and other symptoms involving abdomen and pelvis. Overall, 1,562 patients (1.4 %) underwent a surgical procedure prior to SIRS qualification. Mean APS was 7 ± 6 and mean Elixhauser comorbidity score was 4 ± 7. Supplementary Tables 2 and 3 present patient characteristics stratified by fluid volume.

Serum chloride and in-hospital mortality

The majority of patients ($n = 108{,}110$; 99.3 %) had a baseline serum chloride concentration between 80 and 120 mmol/L. In-hospital mortality was lowest among patients with baseline chloride concentrations of 100–110 mmol/L (3.4 %) and highest among patients with 130–140 mmol/L baseline concentrations (31.1 %). Regression analysis indicated that in-hospital mortality increased sharply in patients with pre-resuscitation baseline serum concentrations ≥110 mmol/L (Supplementary Fig. 2a). Pairwise comparisons revealed that mortality was significantly lower among patients with a 100–110 mmol/L baseline serum chloride concentration versus groups with concentrations ≥110 or 80–100 mmol/L ($P < 0.001$ for all pairwise comparisons). A very small fraction of patients (<1 %) had particularly low baseline chloride (70–80 mmol/L), but the sample size was too small to detect a significant association with mortality versus patients with 100–110 mmol/L baseline concentrations ($P > 0.99$). Regarding peak serum chloride concentration, in-hospital mortality was lowest among patients with peak concentrations in the range of 100–110 mmol/L (3.0 %) and highest among patients with peak concentrations of 140–150 mmol/L (33.3 %; Supplementary Fig. 2b).

Larger positive shifts in serum chloride (i.e. larger increases from baseline) were associated with higher in-hospital mortality rates (Fig. 1), and regression analysis indicated a strong linear relationship ($R^2 = 0.97$; $P < 0.001$). Patients with the smallest increase in serum chloride concentration (0–10 mmol/L) had the lowest observed in-hospital mortality (3.7 %), and mortality increased significantly as the change in serum chloride increased. Mortality rate was 7.2 % among patients with shifts of 10–20 mmol/L, 9.2 % among patients with shifts of 20–30 mmol/L and 9.7 % among patients with shifts of 30–40 mmol/L ($P < 0.001$ for pairwise comparisons versus 0–10 mmol/L group).

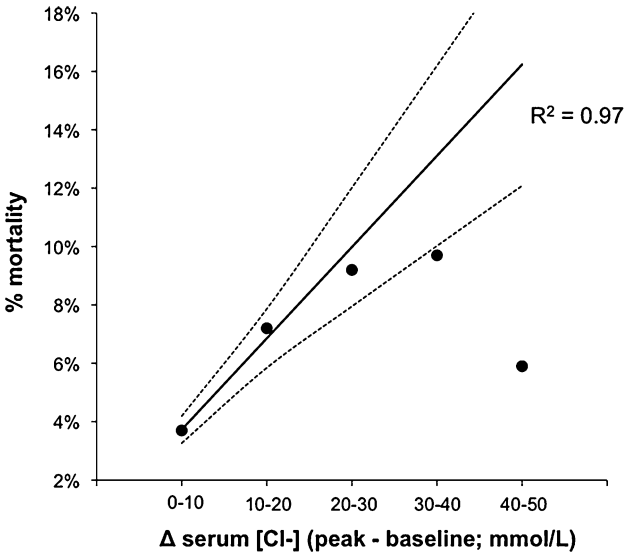

Fig. 1 Relationship between the change in serum chloride concentration (Δ serum [Cl^-]) and in-hospital mortality in patients meeting SIRS criteria and receiving >500 mL IV crystalloid fluids within 2 days of SIRS qualification. Overall, 99.8 % of patients ($n = 109{,}658$) experienced a change in serum chloride of 0–30 mmol/L. Data are fitted with a linear function (*solid line*), weighted on the basis of the number of patients in each Δ serum [Cl^-] group. *Dashed lines* represent 95 % confidence interval

Chloride load and in-hospital mortality: adjustment for fluid volume

Examination of in-hospital mortality versus total chloride received revealed that mortality increased with higher total IV chloride load ($R^2 = 0.91$, $P < 0.001$; Fig. 2a). Mortality was lowest among patients who received low total amounts of chloride (3.5 % among patients receiving 100–200 mmol versus 9.5 % among patients receiving >1,400 mmol; $P = 0.028$). Regression analysis also suggested that larger fluid volumes were associated with higher in-hospital mortality ($R^2 = 0.97$, $P < 0.001$; Fig. 2b). The lowest mortality rate was observed among patients receiving 1,000–2,000 mL IV fluid (3.7 %; $P < 0.05$ for pairwise comparisons with volume groups ≥3,000 mL), while patients receiving 11,000–12,000 mL had the highest observed mortality rate (10.8 %; $P < 0.05$ for pairwise comparisons with volume groups <5,000 mL). Hence, increasing chloride load and total volume appear to be independently associated with higher in-hospital mortality.

Because total fluid volume received—and therefore chloride load—may be associated with severity of illness,

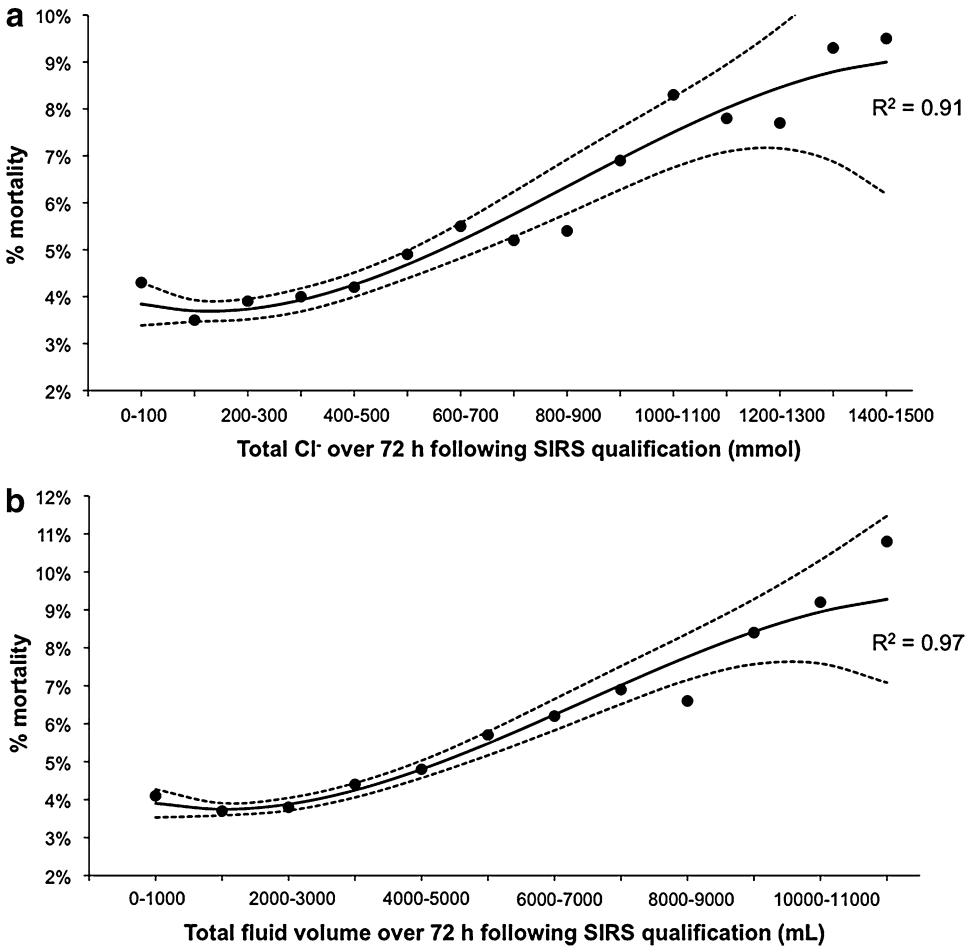

Fig. 2 Relationship between chloride load received within 72 h following SIRS qualification and in-hospital mortality (**a**). Relationship between IV fluid volume received within 72 h of SIRS qualification and in-hospital mortality (**b**). Regression lines (*solid lines*) in both panels represent a cubic polynomial fit and are weighted on basis of the number of patients receiving given amounts of total chloride or IV fluid. *Dashed lines* represent 95 % confidence interval

we examined the relationship between chloride load and in-hospital mortality after accounting for fluid volumes, first by making comparisons within strata of resuscitation fluid volume received, and second by examining the association between volume-adjusted chloride load and mortality. Broadly, mortality tended to increase with greater chloride load within each resuscitation fluid volume stratum (Fig. 3), with the only exception being within patients receiving <1,500 mL. With respect to volume-adjusted chloride load, in-hospital mortality was lowest (2.6 %) among patients receiving 105–115 mmol/L. Regression analysis suggested that mortality increased as patients received volume-adjusted chloride loads ≥105 mmol/L ($R^2 = 0.82$, $P < 0.001$; Fig. 4). Patients with the lowest volume-adjusted chloride loads (<105 mmol/L), who accounted for a small proportion (<2.5 %) of the study population, represented an exception to this trend (mortality decreased as volume-adjusted chloride load increased). However, the trend observed in >97.5 % of the population was that after volume adjustment, mortality rates increased with greater volume-adjusted chloride loads. Mortality OR associated with an incremental 10 mmol/L increase in volume-adjusted chloride load was 0.814 [0.762, 0.870] and 1.095 [1.065, 1.127] for patients with volume-adjusted chloride loads <105 and ≥105 mmol/L, respectively (Fig. 4). Thus, mortality decreased with greater volume-adjusted chloride load up to 105 mmol/L and increased with volume-adjusted chloride loads 105 mmol/L and higher. Severity of illness adjustment using APS did not have a meaningful impact on mortality ORs [<105 mmol/L: 0.888 (0.827, 0.957); ≥105 mmol/L: 1.094 (1.062, 1.127)], suggesting that the apparent association between mortality and volume-adjusted chloride load is not explained by severity of illness. Analysis using a multivariate model (Supplementary Table 4) similarly found mortality ORs of 0.916 [0.844, 0.997] and 1.046 [1.013, 1.079] for patients receiving volume-adjusted chloride loads <105 and ≥105 mmol/L, respectively, after APS adjustment. Post hoc analysis of continuous data below, within, and above the normal chloride range (Supplementary Table 5) revealed that increasing volume-adjusted chloride load was associated with APS-adjusted ORs of 1.000 [0.973, 1.027], 1.027 [0.970, 1.086] and 1.011 [1.008, 1.014] for patients receiving <98, 98–110 and >110 mmol/L, respectively.

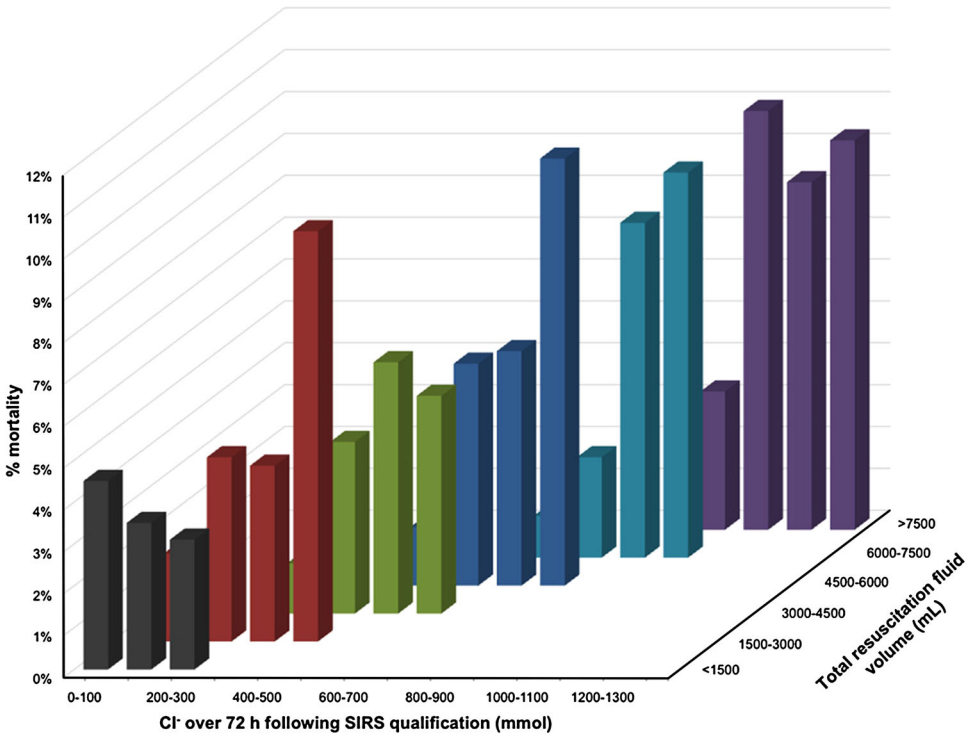

Fig. 3 Relationship between chloride load received via IV resuscitation fluids within 72 h following SIRS qualification and in-hospital mortality, stratified by total resuscitation fluid volume received. In the <1,500 mL group, there was a weak association between increasing total chloride and reduced mortality (weighted linear fit; slope = −0.01, $R^2 = 0.99$). For the 1,500–3,000 through 6,000–7,500 mL groups, there was an increasingly positive association (increased mortality with increasing chloride load) for each incremental volume increase (1,500–3,000 mL: slope = 0.003, $R^2 = 0.11$; 3,000–4,500 mL: slope = 0.01, $R^2 = 0.60$; 4,500–6,000 mL: slope = 0.02, $R^2 = 0.76$; 6,000–7,500 mL: slope = 0.03, $R^2 = 0.89$; >7,500 mL: slope = 0.01, $R^2 = 0.32$)

Examining mortality versus sodium load after accounting for fluid volume showed that mortality tended to increase with sodium load in patients receiving >3,000 mL resuscitation fluids, but there was no association in groups receiving lower volumes (Supplementary Fig. 3). Mortality was lowest among patients receiving a volume-adjusted sodium load of 135–145 mmol/L (Supplementary Fig. 4) [30].

Discussion

This study demonstrates an association between greater amounts of chloride received during crystalloid resuscitation and increased in-hospital mortality, even after controlling for total fluid volume received. While previous studies have compared mortality in patients receiving balanced versus unbalanced crystalloids [11, 16, 22–25], this is, to our knowledge, the first study to specifically examine whether the relationship between crystalloid chloride content and mortality is attributable to the chloride load independent of fluid volume.

The observed association between greater chloride loads and increased in-hospital mortality is not entirely surprising, since the infusion of chloride-rich fluids is itself associated with hyperchloraemia [8–13], which has been associated with a greater likelihood of poor patient outcomes [20, 21]. Consistent with previous reports, this study found elevated mortality rates in patients who would generally be classified as hyperchloraemic [20, 21]. Similarly, large changes in serum chloride concentration, suggesting a shift to a hyperchloraemic state, correlated with greater in-hospital mortality, supporting the idea that maintenance of physiologic serum chloride levels may be important. These findings contribute to the growing observational evidence of the potentially serious clinical impact of using chloride-rich crystalloids. Two recent studies using data from a large US claims database demonstrated an elevated risk of several complications in patients receiving 0.9 % saline versus a balanced crystalloid [18, 23].

In-hospital mortality was observed to increase with greater total chloride loads. Similarly, mortality tended to increase with increased total fluid volume, consistent with findings from the FACTT (Fluid and Catheter Treatment Trial) and trials in surgical patients showing associations between fluid overload and morbidity and mortality [31–33]. Our observations within defined volume strata and based on volume-adjusted total chloride loads indicate that mortality may be related to the chloride load independent of fluid volume. An exception to the trend of increasing mortality within resuscitation fluid volume strata was observed among the lowest volume group (<1,500 mL), which may reflect the low total chloride loads received by patients in this group (0–300 mmol), and further, the importance of appropriate fluid resuscitation in hyperchloraemic patients. The observed trend in patients receiving ≥1,500 mL (increasing mortality with increasing chloride load) may reflect the potential risks of

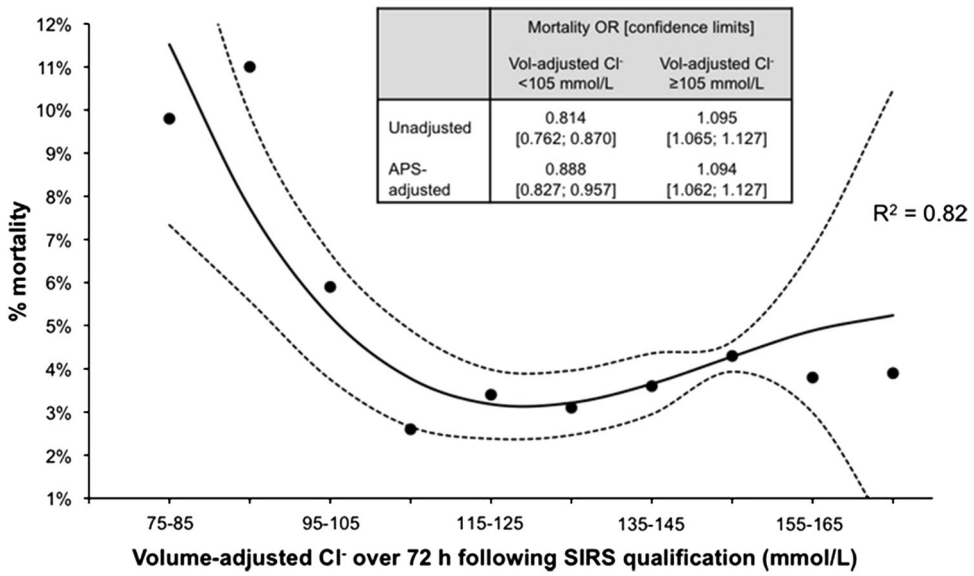

Fig. 4 Relationship between volume-adjusted chloride load received within 72 h following SIRS qualification and in-hospital mortality. Regression line (*solid line*) represents a cubic polynomial fit and is weighted on the basis of the number of patients receiving each given amount of volume-adjusted chloride. *Dashed lines* represent 95 % confidence interval. *Inset table* presents unadjusted and APS-adjusted mortality odds ratio (OR) associated with 10 mmol/L incremental increases in volume-adjusted chloride load for patients with volume-adjusted chloride load <105 and ≥105 mmol/L, respectively. Separate ORs were analysed for patients receiving <105 and ≥105 mmol/L given that (1) >97 % of patients received a volume-adjust chloride load ≥105 mmol/L, (2) lowest mortality was observed in patients receiving 105–115 mmol/L chloride and (3) 105 mmol/L approximates the established upper limit of normal serum chloride concentration [30]

resuscitation with chloride-liberal fluids. With respect to volume-adjusted chloride load, in-hospital mortality was generally low (<4 %) among patients receiving 105–145 mmol/L chloride, with the lowest mortality among patients receiving 105–115 mmol/L. Post hoc analysis found increasing mortality odds with increasing volume-adjusted chloride load >110 mmol/L, indicating potential risks associated with chloride loads exceeding normal serum concentration ranges. These observations are particularly meaningful given that balanced crystalloids with chloride concentrations in the normal physiological range are readily available, though not widely utilized among this patient population, as the large majority (>80 %) of patients primarily receive 0.9 % saline [1, 5]. While increasing fluid volume was associated with increased mortality (Fig. 2b), controlling for total volume does not specifically control for severity of illness. We therefore examined associations between volume-adjusted chloride load and mortality by controlling for severity of illness using the APS. The lack of a meaningful effect on mortality ORs suggests that the association between volume-adjusted chloride load and mortality was not driven by severity of illness.

It is noteworthy that mortality was elevated in the small group of patients (<2.5 % of the study population) who received relatively low volume-adjusted chloride loads (<105 mmol/L). Potential explanations include the receipt of relatively large proportions of dextrose-containing maintenance fluids, which contain lower chloride concentrations, rather than active resuscitation. Particularly high-acuity patients may have died before receiving adequate resuscitation or fluid administration may have been limited because of concerns related to comorbidities such as congestive heart failure in which higher sodium loads are not tolerated and carry a high mortality rate.

Recent evidence indicates risks associated with high sodium loads and suggests that hyperchloraemic metabolic acidosis and hypernatraemia may be independent complications associated with fluid infusion [34]. While our study found a potential association between sodium load and mortality, the ability to fully separate sodium load from volume and tonicity is limited, and this question may warrant further study. Studies examining outcomes in light of relative differences in chloride and sodium load may provide important insights.

While the reasons for the association between increased mortality and elevated chloride levels remain to be fully elucidated, important clinical consequences of hyperchloraemia are known [10, 12, 13, 20, 21, 35]. High serum chloride concentrations following infusion of 0.9 % saline are associated with reduced renal artery flow velocity, renal cortical tissue perfusion and longer time to urination [10, 12, 13]. Additionally, animal studies have implicated hyperchloraemia in effects on the immune system [36, 37], altered blood oxygen binding [38] and organ damage [39].

In summary, this study demonstrates an association between IV chloride load and mortality in hospitalized patients with SIRS, independent of total fluid volume. Given the study's predefined fluid inclusion criteria, our findings may not be generalizable to all SIRS patients. Still, these findings support existing published data suggesting that fluid composition and volume both have important effects on clinical outcomes. Because the study was observational, the associations are hypothesis-generating and highlight the need for randomized controlled trials powered to detect outcome differences in patients resuscitated using different crystalloids. A multicentre study comparing 0.9 % saline and a balanced crystalloid is underway [40]. When viewed together with the existing literature, our findings may not represent evidence that high-chloride solutions are harmful "beyond a reasonable doubt" (they are observational), but the balance of probabilities appears to be shifting away from high-chloride and toward low-chloride solutions for first-line fluid resuscitation of patients with SIRS.

Acknowledgments This study was funded by Baxter Healthcare, Deerfield, IL, USA. The authors thank David Hayashida, Eoin O'Connell and Victor Khangulov of Boston Strategic Partners for statistical support.

Conflicts of interest A.D. Shaw has received payments from Baxter Healthcare Corporation for consulting services and study design. K. Raghunathan declares no conflict of interest. F.W. Peyerl, S.H. Munson and S.M. Paluszkiewicz are employees of Boston Strategic Partners, Inc., funded by Baxter Healthcare Corporation to conduct the study analyses. C.R. Schermer is an employee of Baxter Healthcare. This study was funded by Baxter Healthcare Corporation, Deerfield, IL, USA.

References

1. Lobo DN, Lewington AJ, Allison SP (2013) Basic concepts of fluid and electrolyte therapy. Bibliomed, Melsungen
2. Antonelli M, Bonten M, Chastre J, Citerio G, Conti G, Curtis JR, De Backer D, Hedenstierna G, Joannidis M, Macrae D, Mancebo J, Maggiore SM, Mebazaa A, Preiser JC, Rocco P, Timsit JF, Wernerman J, Zhang H (2012) Year in review in Intensive Care Medicine 2011. II. Cardiovascular, infections, pneumonia and sepsis, critical care organization and outcome, education, ultrasonography, metabolism and coagulation. Intensive Care Med 38:345–358
3. Liu B, Finfer S (2009) Intravenous fluids in adults undergoing surgery. BMJ 338:b2418
4. Powell-Tuck J, Gosling P, Lobo DN, Allison SP, Carlson GL, Gore M, Lewington AJ, Pearse RM, Mythen MG (2011) British consensus guidelines on intravenous fluid therapy for adult surgical patients (GIFTASUP). http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf. Accessed 29 Jan 2014
5. Wan L, Bellomo R, May CN (2007) The effects of normal and hypertonic saline on regional blood flow and oxygen delivery. Anesth Analg 105:141–147
6. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Raibbandari D, Taylor CB, Webb SA, CHEST Investigators, Australiand and New Zealand Intensive Care Society Clinical Trials Group (2012) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 367:1901–1911
7. SAFE Study Investigators, Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh JA, Norton R (2011) Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 37:86–96
8. McFarlane C, Lee A (1994) A comparison of Plasmalyte 148 and 0.9 % saline for intra-operative fluid replacement. Anaesthesia 49:779–781
9. Scheingraber S, Rehm M, Sehmisch C, Finsterer U (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 90:1265–1270
10. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP (2003) (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci 104:17–24
11. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR (2001) Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 93:817–822
12. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ (1999) The effect of intravenous lactated Ringer's solution versus 0.9 % sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 88:999–1003
13. Chowdhury AH, Cox EF, Francis ST, Lobo DN (2012) A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9 % saline and Plasma-Lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 256:18–24
14. Cieza JA, Hinostroza J, Huapaya JA, Leon CP (2013) Sodium chloride 0.9 % versus lactated Ringer in the management of severely dehydrated patients with choleriform diarrhoea. J Infect Dev Ctries 7:528–532
15. Mahler SA, Conrad SA, Wang H, Arnold TC (2011) Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. Am J Emerg Med 29:670–674
16. Berger MM, Pictet A, Revelly JP, Frascarolo P, Chiolero RL (2000) Impact of a bicarbonated saline solution on early resuscitation after major burns. Intensive Care Med 26:1382–1385

17. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK (2011) The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med 39:2419–2424
18. Raghunathan K, Shaw AD, Nathanson B, Stürmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK (2014) Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 42:1585–1591
19. Cho YS, Lim H, Kim SH (2007) Comparison of lactated Ringer's solution and 0.9 % saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. Emerg Med J 24:276–280
20. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS (2013) Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg 117:412–421
21. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR (2011) Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. J Crit Care 26:175–179
22. Mahajan V, Sajan SS, Sharma A, Kaur J (2012) Ringers lactate versus normal saline for children with acute diarrhea and severe dehydration- a double blind randomized controlled trial. Indian Pediatr 49:963–968
23. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA (2012) Major complications, mortality, and resource utilization after open abdominal surgery: 0.9 % saline compared to Plasma-Lyte. Ann Surg 255:821–829
24. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M (2012) Association between a chloride-liberal versus chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 308:1566–1572
25. Young JB, Utter GH, Schermer CR, Galante JM, Phan HH, Yang Y, Anderson BA, Scherer LA (2013) Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. Ann Surg 259:255–262
26. Al-Khafaji A, Webb AR (2004) Fluid resuscitation. Cont Ed Anaesth Crit Care Pain 4:127–131
27. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 43:1130–1139
28. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ (2009) A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 47:626–633
29. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
30. Kratz A, Ferraro M, Sluss PM, Laewandrowski KB (2004) Laboratory reference values. N Engl J Med 351:1548–1563
31. National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Weidemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AFJ, Hite RD, Harabin AL (2006) Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564–2575
32. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lidorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F (2003) Danish study group on perioperative fluid therapy. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg 238:641–648
33. Stewart RM, Park PK, Hunt JP, McIntyre RCJ, McCarthy J, Zarzabal LA, Michalek JE, National Institutes of Health National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network (2009) Less is more: improved outcomes in surgical patients with conservative fluid administration and central venous catheter monitoring. J Am Coll Surg 208:725–735
34. Van de Louw A, Shaffer C, Schaefer E (2014) Early intensive care unit-acquired hypernatremia in severe sepsis patients receiving 0.9 % saline fluid resuscitation. Acta Anaesthesiol Scand 58:1007–1014. doi:10.1111/aas.12368
35. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG (2001) The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 93:811–816
36. Kellum JA, Song M, Almasri E (2006) Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest 130:962–967
37. Kellum JA, Song M, Venkataraman R (2004) Effects of hyperchloremic acidosis on hemodynamics and circulating inflammatory molecules in experimental sepsis. Chest 125:243–248
38. Cambier C, Detry B, Beerens D, Florquin S, Ansay M, Frans A, Clerbaux T, Gustin P (1998) Effects of hyperchloremia on blood oxygen binding in healthy calves. J Appl Physiol 85:1267–1272
39. Pedoto A, Caruso JE, Nandi J, Oler A, Hoffmann SP, Tassiopoulos AK, McGraw DJ, Camporesi EM, Hakim TS (1999) Acidosis stimulates nitric oxide production and lung damage in rats. Am J Respir Crit Care Med 195:397–402
40. The Australian and New Zealand Intensive Care Society Clinical Trials Group (2013) 0.9 % Saline versus Plasma-Lyte 148 for Intensive Care Fluid Therapy (the SPLIT study). ACTRN Trial ID 12613001370796. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365460. Accessed 3 June 2014