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# Impact of intravenous fluid composition on outcomes in patients with systemic inflammatory response syndrome

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## Abstract

**Introduction:** Intravenous (IV) fluids may be associated with complications not often attributed to fluid type. Fluids with high chloride concentrations such as 0.9 % saline have been associated with adverse outcomes in surgery and critical care. Understanding the association between fluid type and outcomes in general hospitalized patients may inform selection of fluid type in clinical practice. We sought to determine if the type of IV fluid administered to patients with systemic inflammatory response syndrome (SIRS) is associated with outcome.

**Methods:** This was a propensity-matched cohort study in hospitalized patients receiving at least 500 mL IV crystalloid within 48 hours of SIRS. Patient data was extracted from a large multi-hospital electronic health record database between January 1, 2009, and March 31, 2013. The primary outcome was in-hospital mortality. Secondary outcomes included length of stay, readmission, and complications measured by ICD-9 coding and clinical definitions. Outcomes were adjusted for illness severity using the Acute Physiology Score. Of the 91,069 patients meeting inclusion criteria, 89,363 (98 %) received 0.9 % saline whereas 1706 (2 %) received a calcium-free balanced solution as the primary fluid.

**Results:** There were 3116 well-matched patients, 1558 in each cohort. In comparison with the calcium-free balanced cohort, the saline cohort experienced greater in-hospital mortality (3.27 % vs. 1.03 %,  $P < 0.001$ ), length of stay (4.87 vs. 4.38 days,  $P = 0.016$ ), frequency of readmission at 60 (13.54 vs. 10.91,  $P = 0.025$ ) and 90 days (16.56 vs. 12.58,  $P = 0.002$ ) and frequency of cardiac, infectious, and coagulopathy complications (all  $P < 0.002$ ). Outcomes were defined by administrative coding and clinically were internally consistent. Patients in the saline cohort received more chloride and had electrolyte abnormalities requiring replacement more frequently ( $P < 0.001$ ). No differences were found in acute renal failure.

**Conclusions:** In this large electronic health record, the predominant use of 0.9 % saline in patients with SIRS was associated with significantly greater morbidity and mortality compared with predominant use of balanced fluids. The signal is consistent with that reported previously in perioperative and critical care patients. Given the large population of hospitalized patients receiving IV fluids, these differences may confer treatment implications and warrant corroboration via large clinical trials.

**Trial registration:** NCT02083198 [clinicaltrials.gov](http://clinicaltrials.gov); March 5, 2014

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## Introduction

The concentration of chloride in 0.9 % saline is supra-physiological [1] and infusion of moderate to large volumes has been shown to produce hyperchloremic acidosis [2–12]. Hyperchloremic acidosis has been associated with adverse physiological effects in both animals and human volunteers [2, 9, 10, 13, 14]. However, small human trials have failed to show detrimental clinical outcomes when it has been compared with balanced crystalloids [15–18].

In animals, experimental hyperchloremic acidosis induces shock, is proinflammatory, and reduces survival in sepsis [19–22]. Recent studies have suggested that both hyperchloremia [23] and infusion of chloride-rich fluids [24, 25] have detrimental effects on clinical outcomes in postoperative and critically ill patients. A propensity-matched study of surgical patients who received 0.9 % saline or a calcium-free balanced crystalloid on the day of surgery showed a higher proportion of 0.9 % saline recipients developing complications [24]. A similar analysis comparing balanced crystalloids with 0.9 % saline in patients with sepsis found that balanced crystalloids were associated with improved survival [26]. A study evaluating the impact of restricting high-chloride fluids in intensive care unit (ICU) patients showed that chloride restriction led to a lower incidence of acute kidney injury and need for renal replacement therapy, but showed no differences in hospital mortality or length of stay [27].

Although there is a growing body of evidence to suggest that 0.9 % saline may adversely impact outcomes in critically ill and surgical patients, studies evaluating the impact of high-chloride fluids in hospitalized patients with lower illness severity are lacking. The purpose of this study was to determine if the hazards associated with 0.9 % saline that appear to occur in surgical and ICU patients also occur in a broader patient population receiving intravenous (IV) fluid therapy. The aim of the study was to determine whether, among patients with systemic inflammatory response syndrome (SIRS), use of 0.9 % saline as an early fluid choice was associated with adverse outcomes, when compared with a regimen composed of more physiologic IV solutions.

## Methods

### Overview

We examined a large US electronic health record (EHR) database (HealthFacts®, Cerner Corp., Kansas City, MO, USA) to identify hospitalized patients who met at least two SIRS criteria and received at least 500 mL of IV fluid within 48 hours of first developing SIRS. We included patients aged  $\geq 18$  years with a length of stay of at least 24 hours. We defined SIRS as the presence of tachycardia [heart rate (HR)  $>90$  bpm] along with at

least one of the following on the same day: (1) temperature  $>38$  °C or  $<36$  °C, (2) respiratory rate  $\geq 20$  breaths/minute or PaCO<sub>2</sub>  $\leq 32$  mmHg, or (3) leukocytes  $\geq 12,000$  or  $\leq 4,000$  cells/mm<sup>3</sup>. This modified SIRS definition was chosen because HR was the most populated field of the SIRS criteria and allowed us to initially select patients from a dataset of  $>1$  million subjects. Two propensity-matched cohorts were created based upon the type of isotonic crystalloid received. The study protocol and analysis plan were approved (prior to data extraction) by the Duke University institutional review board with waiver of requirement for written informed consent, and was registered on the clinicaltrials.gov website (NCT02083198).

### Inclusion criteria and cohorts

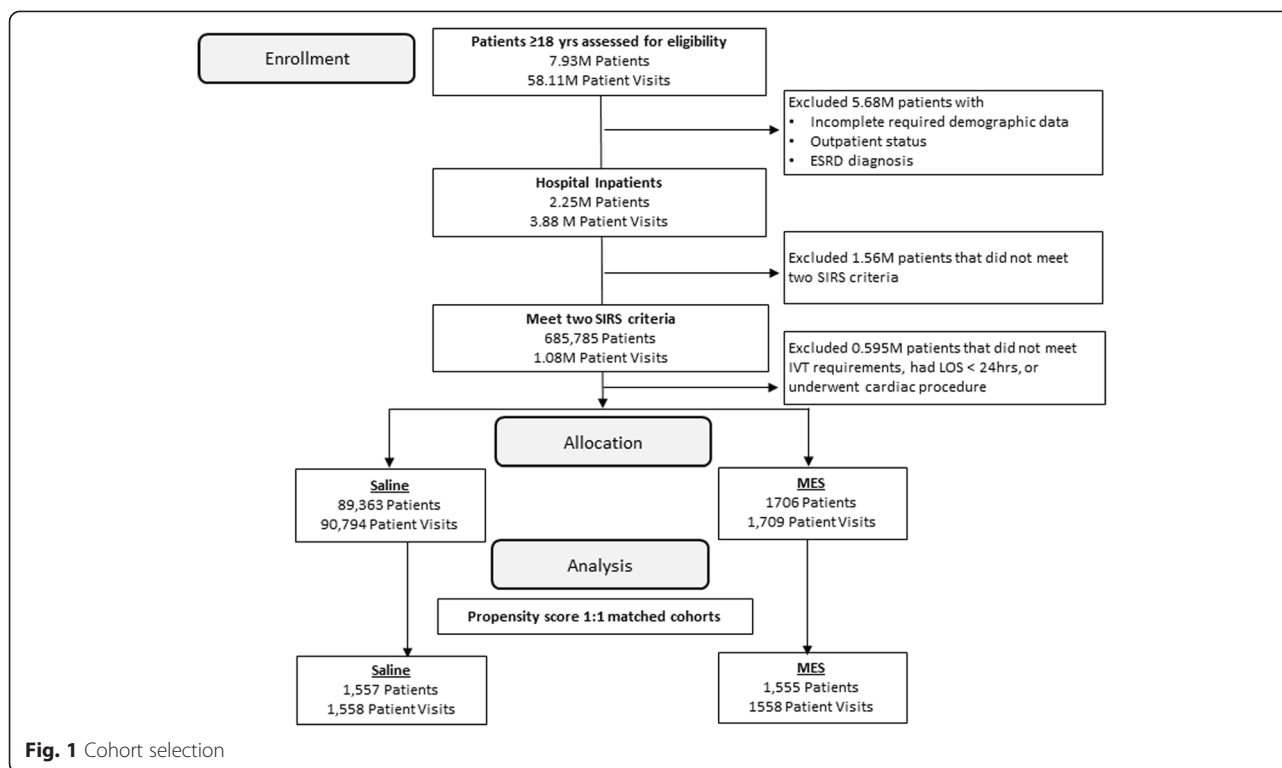
Included patients were required to receive  $\geq 500$  mL of the cohort-qualifying crystalloid solution within 2 days of meeting SIRS criteria. In order to determine if the associations with fluid type were similar to findings in the surgical population, patients selected for the balanced fluid cohort must have received  $\geq 500$  mL of a calcium-free balanced crystalloid (Plasma-Lyte® [Baxter Healthcare, Deerfield, IL, USA] or Normosol® [Hospira, Lake Forest, IL, USA]). Patients selected for the saline cohort must have received  $\geq 500$  mL 0.9 % saline and must not have received any calcium-free balanced fluid (Fig. 1). To capture the full picture of crystalloid administered, patients in either cohort were also allowed to have received additional balanced fluids or saline in the 72 hours following SIRS criterion with the exception that the saline cohort could not receive calcium-free balanced fluid. These other fluid types and volumes for non-dextrose-containing IV fluid (calcium-free balanced, 0.9 % saline, lactated Ringer's, and 0.45 % saline) were summed over a 3-day time period post SIRS qualification. IV fluid orders for bag volumes  $\leq 250$  mL were not included in the total volumes because they are frequently used for drug admixture.

### Exclusion criteria

Patients receiving  $>1$  L of IV fluid the day prior to SIRS qualification were excluded. Also excluded were those who had cardiac surgery (part of another study), a diagnosis of end-stage renal disease, or receipt of any colloid or hypertonic saline.

### Data source

HealthFacts® is a de-identified EHR database that is an aggregate of administrative data [International Classification of Diseases, Ninth Revision (ICD-9)] and clinical/quantitative data (medication and diagnostic test orders and laboratory results). A subset of inpatients from January 1, 2009, through March 31, 2013, was utilized.



### Data processing

Analysis inclusion required the presence of patient identifier, age, race, and gender, admission and discharge date/time, discharge status and SIRS qualification, and IV fluid data. Diagnoses and procedures were captured if present, as well as microbiology tests if positive. Laboratory results were available and the absence of a laboratory value was assumed normal. For multiple readings, the most abnormal reading was utilized.

### Outcomes

Outcomes were evaluated by administratively coded data and corroborated by clinically defined parameters. Mortality was the primary outcome of interest. Secondary outcomes, chosen based on animal models [13, 14, 19–22], small human trials [2–5, 9, 10, 15–18] and physiological argument, included in-hospital complications, electrolyte and acid–base disturbances, length of stay, and readmission. Administrative outcomes were defined by ICD-9 diagnosis codes and categorized as: (1) cardiac, (2) hemorrhage, (3) infection, (4) gastrointestinal (GI), (5) neurologic, (6) acute renal failure, (7) respiratory failure, and (8) new organ failure (a composite of new organ system failure). Outcomes were determined by codes not denoted as “present on admission” (Table S1 in Additional file 1).

Clinical outcomes were operationally defined and grouped as follows (Table S2 in Additional file 2). Cardiac complications: (1) dysrhythmia – infusion of IV antiarrhythmics on day of SIRS qualification through 3 days,

(2) cardiac stress – abnormal troponin, (3) congestive heart failure (CHF) – order for ECHO or brain natriuretic peptide (BNP) >600 pg/mL, and same day diuretic use, (4) cardiac failure – vasopressor use within 3 days of SIRS qualification, and (5) cardiac Sequential Organ Failure Assessment (SOFA) score [28]. Hemorrhage complications: (1) hemoglobin decrease of >20 g/L/24 hours, (2) transfusion by ICD-9 procedure codes, (3) coagulopathy by abnormal prothrombin time-international normalized ratio (PT-INR) in the absence of warfarin, thrombocytopenia of <150,000 × 10<sup>9</sup>/l, or abnormal D-dimer, (4) SOFA coagulation score. Infection was defined by leukocyte count >12,000 × 10<sup>9</sup> cells/l within 1 day of date of culture and administration of antibiotics within 3 days of culture. Positive cultures were specific to each infection: (1) pneumonia-tracheal aspirate or bronchoalveolar lavage, (2) bacteremia/sepsis by blood culture, and (3) urinary tract infection by urine culture. Respiratory failure was assessed using SOFA pulmonary scores [28]. GI complications were defined by: (1) acute cholecystitis, and (2) SOFA liver score. Acute kidney injury was defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria using serum creatinine only [29]. The baseline creatinine used was the lowest creatinine in the 7 days prior to the SIRS qualifying event.

Electrolytes monitored included magnesium, potassium, sodium, and ionized calcium. Electrolytes were designated as abnormal when outside of the following ranges: (1) Mg <0.70 mmol/L; >1.0 mmol/L, (2) K <3.5 mmol/L; >5.0

mmol/L, (3) Na <136 mmol/L; >145 mmol/L, (4) ionized Ca <1.1 mmol/L; >1.4 mmol/L. Patients with low magnesium, potassium, or ionized calcium who received IV magnesium, IV calcium, or IV or oral potassium were counted as having received replacement. Acidosis was defined operationally and measured in three ways: (1) hyperchloremic acidosis: arterial blood pH <7.35 and serum chloride >110 mmol/L, (2) metabolic acidosis as pH <7.35 and bicarbonate <22 mmol/L, (3) lactic acidosis as venous or arterial lactate >2.0 mmol/L.

#### Comorbidities and severity of illness

Comorbidities were defined using ICD-9 diagnostic codes and collated using the Elixhauser algorithm [30]. To ensure mutual exclusivity of the comorbidities and outcomes, the renal failure unspecified (ICD-9 code 586) comorbidity was removed because it overlapped with the administrative outcome. Peripheral vascular disease was modified to remove ICD-9 code 557.9 due to overlap with a GI administrative outcome. The electrolyte abnormalities comorbidity was not included because it was a measured outcome.

To further evaluate severity of illness, the Acute Physiology Score (APS) from the Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated for each patient [31] using data collected on the day of SIRS qualification and 1 day prior, using the higher of the two. Where clinical data were missing for an APS variable, it was assumed to be normal.

#### Controlling for bias and confounding: propensity scores, cohort matching and adjusted outcomes models

To account for potential selection bias, we developed a propensity score [32] representing the probability that a patient would receive balanced crystalloid based on patient and hospital characteristics and comorbidities. The score was calculated using logistic regression with backward inclusion of the covariates. The patients in the saline and balanced cohorts were then matched 1:1 using a case-control greedy matching algorithm [33].

All administrative and clinical outcomes were compared between the matched cohorts. Continuous characteristics were compared by Student's *t* test and categorical parameters were compared by  $\chi^2$  test. A *P* value of less than 0.05 was considered statistically significant. To account for the impact of severity of acute illness, the APS was used to adjust all outcomes. In addition, outcome models were also adjusted for variables that were different (*P* <0.1) between cohorts after propensity matching. Outcome models are reported as odds ratios (ORs) with 95 % confidence intervals (CIs). Data were analyzed using SAS/Base software, Version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

Propensity scoring was able to match 1558 of 1709 patients receiving balanced fluid to patients receiving saline (Table 1). The hospital characteristics that remained significantly different after the match were admission source, payor, and census region. For patient characteristics, the frequency for CHF was greater in the saline cohort, and hypertension greater in the balanced cohort. Post-match APS scores remained significantly different, hence the above hospital and patient characteristics that remained different at a *P* <0.1 and APS were used to adjust the outcome models.

The median amount of fluid received over 72 hours after SIRS qualification was similar in both cohorts (Table 2). Patients in both groups received a combination of 0.45 % saline, lactated Ringer's, and 0.9 % saline. Patients in the calcium-free balanced cohort received a significantly lower mean chloride load (112 mmol/L vs. 147 mmol/L), reflecting the chloride content of their early predominant IV fluid.

#### Unadjusted outcomes

Table 3 shows the administrative outcomes demonstrating that calcium-free balanced fluid use was associated with a lower rate of major complications. Specifically, patients receiving calcium-free balanced fluid experienced fewer cardiac, respiratory, infectious, and new organ failure complications. Among the significant outcome differences, the most frequent cardiac complication was atrial fibrillation, the most frequent respiratory complication was acute respiratory failure, the most frequent infectious complication was pneumonia followed by sepsis, and the most frequent new organ failure was acute renal failure, followed by congestive heart failure. Although acute renal failure contributed to the composite of new organ failure, by itself it was not significantly lower in the calcium-free balanced cohort. In addition, no differences were found in administrative outcomes for hemorrhage, GI, or neurological complications.

Table 3 also shows the clinical outcomes. Calcium-free balanced fluid use was associated with lower mortality, shorter hospital stay, lower 60- and 90-day readmission rates, and a lower rate of major complications. The calcium-free balanced group had significantly fewer cardiac complications as measured by dysrhythmias, cardiac stress, and congestive heart failure (BNP and diuretic use definition). There were fewer patients with infectious complications of pneumonia, sepsis, and line infections. SOFA scoring showed that cardiac, liver, and hematologic failure were significantly lower in balanced patients (Table S3 in Additional file 3). Although there was a difference in coagulopathy favoring calcium-free balanced fluid, there was no difference in hemoglobin decrease. Acute kidney injury was not different between groups by

**Table 1** Matched baseline hospital and patient characteristics for balanced and saline cohorts

Patient demographics	Saline n = 1558	Balanced n = 1558	P value (two-sided)
Age group <sup>a</sup>			0.43
18–35	16.88 (263)	17.97 (280)	
36–50	19.06 (297)	19.45 (303)	
51–64	25.8 (402)	27.15 (423)	
65–80	27.54 (429)	26.44 (412)	
80+	10.72 (167)	8.99 (140)	
Gender			0.13
Male	44.09 (687)	41.46 (646)	
Female	55.91 (871)	58.54 (912)	
Race			0.56
Black	11.62 (181)	10.46 (163)	
Other	14.44 (225)	14.25 (222)	
White	73.94 (1152)	75.29 (1173)	
Bed size			0.06
0–199	9.88 (154)	9.18 (143)	
200–399	39.99 (623)	44.22 (689)	
400+	50.13 (781)	46.6 (726)	
Admission source			<0.001
Emergency	1.03 (16)	0.71 (11)	
Healthcare facility	5.07 (79)	7.83 (122)	
Non-healthcare facility	71.69 (1117)	74.01 (1153)	
Other/Unknown	22.21 (346)	17.46 (272)	
Admission type			0.09
Elective	52.37 (816)	56.1 (874)	
Emergency	47.37 (738)	43.77 (682)	
Other/Unknown	0.26 (4)	0.13 (2)	
Payor			0.03
Commercial	13.22 (206)	16.56 (258)	
Medicare/Medicaid	37.48 (584)	37.03 (577)	
Other	49.29 (768)	46.41 (723)	
Urban			0.09
Yes	98.27 (1531)	98.97 (1542)	
No	1.73 (27)	1.03 (16)	
Teaching			0.09
Yes	85.43 (1331)	87.48 (1363)	
No	14.57 (227)	12.52 (195)	
Census region			0.002
Northeast	65.53 (1021)	59.82 (932)	
South	10.85 (169)	11.3 (176)	
West	23.62 (368)	28.88 (450)	

**Table 1** Matched baseline hospital and patient characteristics for balanced and saline cohorts (*Continued*)

	15.53 (242)	14.96 (233)	0.65
Patients with surgical procedures <sup>b</sup>			
Congestive heart failure	3.85 (60)	2.37 (37)	0.02
Valvular heart disease	1.93 (30)	1.22 (19)	0.11
Pulmonary circulation disease	0.26 (4)	0.26 (4)	1.00
Peripheral vascular disease	2.82 (44)	2.57 (40)	0.67
Paralysis	0.9 (14)	0.77 (12)	0.69
Other neurological disorders	3.27 (51)	3.15 (49)	0.84
Chronic pulmonary disease	7.96 (124)	9.11 (142)	0.25
Diabetes w/o chronic complications	7 (109)	7.96 (124)	0.31
Diabetes w/chronic complications	1.86 (29)	1.28 (20)	0.20
Hypothyroidism	3.15 (49)	3.98 (62)	0.21
Renal failure	2.95 (46)	2.25 (35)	0.22
Liver disease	0.96 (15)	1.48 (23)	0.19
Acquired immune deficiency syndrome	0.19 (3)	0.19 (3)	1.00
Lymphoma	1.03 (16)	0.39 (6)	0.03
Metastatic cancer	0.64 (10)	0.77 (12)	0.67
Solid tumor w/o metastasis	1.73 (27)	1.8 (28)	0.89
Rheumatoid arthritis/collagen vas	2.7 (42)	1.73 (27)	0.07
Coagulopathy	1.09 (17)	1.35 (21)	0.51
Obesity	7.12 (111)	8.66 (135)	0.11
Weight loss	1.93 (30)	1.41 (22)	0.26
Chronic blood loss anemia	1.28 (20)	1.35 (21)	0.88
Deficiency anemias	4.24 (66)	5.01 (78)	0.31
Alcohol abuse	1.93 (30)	2.12 (33)	0.70
Drug abuse	1.6 (25)	1.35 (21)	0.55
Psychoses	1.22 (19)	1.48 (23)	0.53
Depression	7.64 (119)	7.25 (113)	0.68
Hypertension	17.2 (268)	22.08 (344)	<0.001

<sup>a</sup>Age used as a continuous variable in the propensity score model<sup>b</sup>Surgical procedure not used within the propensity score model

KDIGO stage. Length of hospital stay was 0.48 days shorter in the calcium-free balanced group (4.38 vs. 4.86 days,  $P = 0.016$ ). Readmission data showed a 30-day re-admission rate of 7.6 % in the balanced cohort and 9.5 % in the saline cohort ( $P = 0.06$ ). The 60- and 90-day re-admission rates were significantly lower in the balanced cohort vs. saline (10.9 % vs. 13.5 % ( $P = 0.025$ ) and 12.6 % vs. 16.6 % ( $P = 0.002$ ) at 60 and 90 days, respectively).

The frequency of electrolyte abnormalities was lower for balanced patients. Moreover, the percentages of patients with a low serum magnesium and low serum potassium receiving replacement were lower in the



**Table 2** Seventy-two-hour fluid volumes and chloride load by matched cohort

Matched 1:1 Calcium-free balanced: 0.9 % saline cohort fluids					
	Calcium-free balanced <sup>a</sup>	0.45 % Saline	Lactated Ringer's	0.9 % Saline	Totals <sup>b</sup>
Calcium-free balanced cohort					
+ n (%)	1558 (100 %)	73 (4.7 %)	548 (35.2 %)	857 (55.6 %)	1558 (100 %)
Average mmol/L	178.4	88.4	172.8	232.3	112.4
Median mmol/L	98	77 .0	109	154	109.2
Average vol. (median)	1.8 L (1.0 L)	1.1 L (1.0 L)	1.6 L (1.0 L)	1.5 L (1.0 L)	3.3 L (2.0 L)
Vol. range	0.5–10.4 L	0.4–3.0 L	0.5–13.5 L	0.5–16.0 L	0.5–19.8 L
0.9 % Saline cohort					
n (%)	Exclusion criteria	54 (3.5 %)	348 (22.3 %)	1558 (100 %)	1558 (100 %)
Average mmol/L		89.3	219	246.5	147.4
Median mmol/L		77	174.4	154	154.0
Average vol. (median)		1.2 L (1.0 L)	2.0 L (1.6 L)	1.6 L (1.0 L)	2.1 L (2 L)
Vol. range		0.5–4.0 L	0.3–10.3 L	0.5–11.6 L	0.5–12.0 L

<sup>a</sup>Note n represents number of patients in the cohort receiving the particular fluid i.e., 73 patients in the calcium-free cohort received 0.45 % saline

<sup>a</sup>Calcium-free balanced crystalloid (e.g., Plasma-Lyte or Normosol: Na 140 mmol/L, Cl 98 mmol/L, K 5.0 mmol/L, Mg 1.5 mmol/L, gluconate 23 mmol/L, acetate 27 mmol/L)

<sup>b</sup>Monitored fluids (calcium-free balanced, 0.45 % saline, lactated Ringer's, 0.9 % saline)

balanced fluid cohort ( $P < 0.001$ ). In addition, the frequency of hyperkalemia was lower ( $P = 0.012$ ) in the balanced fluid cohort.

The different measures of acidosis showed that hyperchloremic acidosis and metabolic acidosis (as defined by low pH and low bicarbonate) were more frequent in the saline cohort (both  $P < 0.001$ ). Although the percentage of patients with lactic acidosis was not different between cohorts (0.71 % saline vs. 0.26 % balanced;  $P = 0.07$ ), more patients receiving saline had lactate levels ordered (5.3 % saline vs. 1.4 % balanced,  $P < 0.001$ ).

### Model adjustment

Figure 2 shows the administrative and clinical outcomes unadjusted and adjusted for APS and variables with a  $P < 0.10$  post-match. APS differed between groups post-match (4.77 saline vs. 4.37 calcium-free balanced,  $P < 0.001$ ). The only administrative outcome that became nonsignificant when adjusted for APS and incompletely matched variables was 60-day readmission. Adjustment of the clinical outcomes affected hyperkalemia and hypocalcemia, requiring replacement and metabolic acidosis, such that they were no longer significant. No administrative or clinical outcome adjusted for APS significantly favored saline.

### Discussion

This observational study provides further support of a possible signal of harm associated with 0.9 % saline, which may be avoided by the use of more physiological fluids. This study evaluated a broader population than our study of surgical patients and corroborated many of

the findings [24]. It appears that the use of saline in patients with SIRS is associated with increased mortality, increased cardiac, infectious, and coagulopathy complications, and an increased need for electrolyte replacement. The inclusion of outcomes measured using clinically defined parameters in this study further strengthens these findings and validates our prior analyses of administrative datasets [24]. Importantly, none of the administrative or clinical outcomes favored the use of 0.9 % saline.

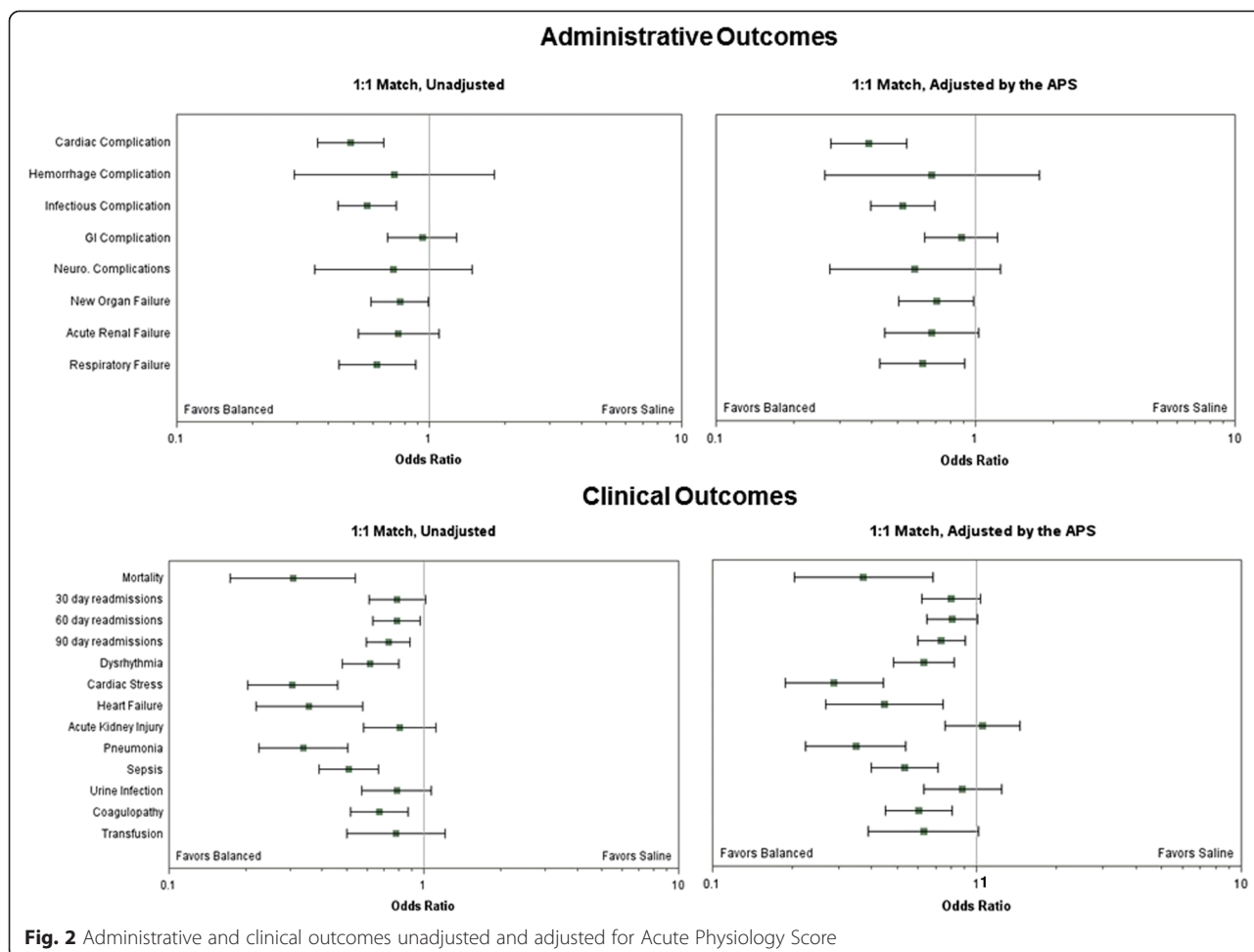
As opposed to our study of major abdominal surgery [24] where we evaluated patients who received exclusively saline or calcium-free balanced fluid, here, although we selected the cohorts based on receipt of calcium-free balanced fluid or saline early in relation to the SIRS event, we intentionally included all non-dextrose-containing crystalloids to make our analysis more generalizable with clinical practice, wherein clinicians use many different types of fluids. Both cohorts received a combination of fluids, but the saline patients did not receive calcium-free balanced fluids. Although many patients in both cohorts received a mix of such that just over one-half of patients in the balanced cohort received saline and roughly 22–35 % in both groups received Ringer's lactate, the initial fluid choice of balanced versus unbalanced resulted in a substantial difference in the ultimate chloride load delivered. We speculate the important exposure difference is likely delivered chloride load, a concept which supports our findings from the larger dataset of 98,000 patients that chloride and volume contribute independently to mortality [25].

In this study, we failed to observe a difference in renal failure/acute kidney injury by ICD-9 coding or KDIGO scoring. We interpret the lack of corroboration of other

**Table 3** Administrative and clinical outcomes by fluid cohort

Outcome/Complication	Saline (n = 1558) % (n)	Balanced (n = 1558) % (n)	Unadjusted odds ratio (95 % confidence interval)	Adjusted odds ratio (95 % confidence interval)
<b>Administrative outcomes</b>				
Cardiac	8.66 (135)	4.43 (69)	0.488 (0.362–0.659)	0.51 (0.378–0.689)
Hemorrhage	0.71 (11)	0.51 (8)	0.726 (0.291–1.809)	0.781 (0.311–1.961)
Infectious	10.14 (158)	6.03 (94)	0.569 (0.436–0.742)	0.618 (0.471–0.809)
Gastrointestinal	5.46 (85)	5.13 (80)	0.938 (0.685–1.284)	0.969 (0.707–1.328)
Neurologic	1.16 (18)	0.83 (13)	0.72 (0.352–1.474)	0.817 (0.395–1.69)
Acute renal failure	4.36 (68)	3.34 (52)	0.757 (0.524–1.093)	0.917 (0.625–1.344)
Respiratory failure	5.46 (85)	3.47 (54)	0.622 (0.439–0.882)	0.692 (0.485–0.986)
New organ failure	9.11 (142)	7.12 (111)	0.765 (0.59–0.991)	0.872 (0.667–1.141)
<b>Clinical outcomes</b>				
Hospital mortality	3.27 (51)	1.03 (16)	0.307 (0.174–0.54)	0.378 (0.211–0.676)
30-day readmissions	9.5 (148)	7.64 (119)	0.788 (0.612–1.014)	0.802 (0.622–1.032)
60-day readmissions	13.54 (211)	10.91 (170)	0.782 (0.63–0.97)	0.798 (0.643–0.991)
90-day readmissions	16.56 (258)	12.58 (196)	0.725 (0.593–0.886)	0.741 (0.606–0.907)
<b>Cardiac</b>				
Dysrhythmia	10.65 (166)	6.87 (107)	0.618 (0.48–0.797)	0.649 (0.502–0.838)
Cardiac stress	6.42 (100)	2.05 (32)	0.306 (0.204–0.458)	0.341 (0.226–0.515)
Heart failure	4.04 (63)	1.48 (23)	0.356 (0.219–0.576)	0.401 (0.246–0.653)
<b>Hemorrhage/Hematologic</b>				
Coagulopathy <sup>a</sup>	11.09 (150)	7.71 (106)	0.67 (0.516–0.87)	0.717 (0.55–0.934)
Received blood transfusion	2.92 (46)	2.27 (36)	0.777 (0.5–1.209)	0.851 (0.544–1.33)
Bleeding	20.09 (313)	19.96 (311)	0.992 (0.832–1.182)	1.074 (0.897–1.286)
<b>Infectious</b>				
Pneumonia	6.03 (94)	2.12 (33)	0.337 (0.225–0.504)	0.393 (0.259–0.596)
Sepsis	10.53 (164)	5.65 (88)	0.509 (0.389–0.666)	0.568 (0.431–0.75)
Urinary tract infection	5.91 (92)	4.69 (73)	0.783 (0.571–1.074)	0.904 (0.653–1.252)
Line infection	0.77 (12)	0	-	-
<b>Gastrointestinal</b>				
Cholecystitis	4.75 (74)	3.53 (55)	0.734 (0.514–1.048)	0.836 (0.58–1.203)
<b>Renal</b>				
Acute kidney injury	5.46 (85)	4.43 (69)	0.803 (0.580–1.112)	0.920 (0.658–1.286)
<b>Electrolyte abnormalities</b>				
Low magnesium with replacement	4.36 (68)	2.12 (33)	0.474 (0.311–0.723)	0.546 (0.355–0.84)
High magnesium	4.36 (68)	3.4 (53)	0.772 (0.535–1.113)	0.95 (0.647–1.393)
Low potassium with replacement	14.12 (220)	7.51 (117)	0.494 (0.39–0.625)	0.551 (0.429–0.706)
High potassium	9.44 (147)	6.87 (107)	0.708 (0.546–0.918)	0.813 (0.621–1.066)
Low sodium	39.41 (614)	30.62 (477)	0.678 (0.585–0.787)	0.707 (0.608–0.822)
High sodium	7 (109)	6.03 (94)	0.854 (0.642–1.135)	1.004 (0.746–1.351)
Low calcium with replacement	1.28 (20)	0.96 (15)	0.748 (0.381–1.466)	1.052 (0.517–2.14)
<b>Metabolic acidosis</b>				
Lactic (pH and lactate)	0.71 (11)	0.26 (4)	0.362 (0.115–1.139)	0.528 (0.161–1.728)
Metabolic (pH and bicarbonate)	2.76 (43)	1.22 (19)	0.435 (0.252–0.75)	0.617 (0.342–1.115)
Hyperchloremic (pH and chloride)	3.47 (54)	1.22 (19)	0.344 (0.203–0.583)	0.449 (0.256–0.786)

<sup>a</sup>Excluded patients receiving warfarin



**Fig. 2** Administrative and clinical outcomes unadjusted and adjusted for Acute Physiology Score

studies showing increased risk for acute kidney injury or renal failure with saline as these patients may have been at overall lower baseline risk than the major surgery and critically ill patients, and hence may have been better able to deal with the hazard. The frequency of elevated creatinine was low (3–4 %) and hence there may be no effect of fluid type on renal risk at the volumes administered in this study. Indeed, in healthy rats, exposure to saline had no effect on kidney function, whereas in animals with sepsis the same volumes resulted in worsening of acute kidney injury [22].

Two criticisms of our prior study [24] were that patients in the saline cohort received more blood and more fluid, which may have driven the worse outcomes. However, in the current study, there was no difference in the frequency of blood transfusion, and the median fluid volumes were similar, but complication rates still favored balanced fluid. Our findings support Raghunathan’s study of patients with sepsis, which showed that as the proportion of saline increased, mortality increased, and this association appeared to be independent of volume [26]. In the present study, the calcium-free balanced cohort received a substantially

lower chloride load, lending support for the concept that mortality and complications are related to fluid composition and not solely to the fluid volume received per se.

Access to clinical data allowed us to provide face validity to the concept that hyperchloremic acidosis was also associated with a higher rate of complications. Our findings support McCluskey’s recent study showing an association of hyperchloremia with increased mortality [23]. These investigators reported mortality rates of 3.0 % in their hyperchloremic group and 1.9 % in their normochloremic group [23], quite similar to our findings of 3.3 % mortality in the saline cohort versus 1.1 % in the calcium-free balanced cohort.

The coagulation abnormalities seen in the SOFA score and by laboratory measures are consistent with abnormalities seen in trauma patients receiving saline [34] and with lower transfusion rates found in surgical patients receiving physiological fluids [17, 24]. However, the clinical implications of these abnormalities are unclear since transfusion did not differ between cohorts.

We believe an important implication of these data regards the exposed population. Intravenous fluid therapy



is one of the most common inpatient interventions prescribed, and 0.9 % saline is the most common fluid used around the world [35, 36]. Thus, if there is a hazard associated with 0.9 % saline, then it could affect large numbers of patients. Given the absence of evidence supporting the use of 0.9 % saline, we believe its use should be limited to the few indications where it is likely of value (e.g., hypovolemic hypochloremic alkalosis).

Observational analyses are inevitably limited by bias and confounding. We attempted to minimize confounding by using a robust propensity-matching algorithm based on potential confounders at the hospital and patient level. For the administrative outcomes, we ensured that outcomes did not overlap with comorbidity codes. The array of patient and hospital information available should have minimized residual effects from unmeasured confounders. Moreover, severity of illness and inadequately matched potential confounders were used to adjust the outcomes. Confounding by indication should have been minimized by our timing of treatment related to the SIRS episode.

The clinical outcomes could be considered more robust than the administrative outcomes, but they are not perfect. The use of the electronic health record did not allow us to obtain results of items such as electrocardiograms (ECGs) or imaging findings in order to fully inform clinical definitions, but we do consider the use of laboratory data and medications to be robust support corroborating the administrative data.

## Conclusions

This evaluation of patients with SIRS receiving crystalloids of different composition adds to the growing body of real-world data showing that 0.9 % saline may not be innocuous when used for volume replacement. These observational studies have generated sufficient questions to warrant a large-scale clinical trial. The recent UK National Institute for Health and Care Excellence guidelines on intravenous fluid therapy [37] recognized the potential hazards of large-volume infusions of 0.9 % saline, and in the absence of large-scale randomized trials, it recommended further research in the area. Although this study does not elucidate the mechanisms leading to the findings, it contributes to the body of research evaluating the potential hazards of 0.9 % saline and its mitigation via the use of commonly available alternative solutions.

## Key messages

- Fluids with high chloride concentrations such as 0.9 % saline have been associated with adverse outcomes in surgery and critical care. Understanding the association between fluid type and outcomes in less ill hospitalized patients may inform selection of fluid type in clinical practice.

- In a large electronic health record, the early use of 0.9 % saline in patients with SIRS was associated with significantly greater morbidity and mortality compared with predominant use of balanced fluids.

## Additional files

**Additional file 1: Table S1.** Summary of administrative outcomes ICD-9 diagnosis and procedure code definitions. This table summarizes the administrative outcomes by ICD-9 diagnosis and procedure codes, grouped by category. (DOCX 26 kb)

**Additional file 2: Table S2.** Summary of clinical outcomes definitions and criteria. This table summarizes and defines clinical outcomes, grouped by category. (DOCX 18 kb)

**Additional file 3: Table S3.** SOFA outcomes by treatment group. This table shows the prevalence of SOFA outcomes, categorized by treatment group. (DOCX 12 kb)

## Abbreviations

APS: Acute Physiology Score; BNP: brain natriuretic peptide; CHF: congestive heart failure; EHR: electronic health record; GI: gastrointestinal; ICD-9: International Classification of Diseases, Ninth Revision; ICU: intensive care unit; IV: intravenous; SIRS: systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment.

## Competing interests

AD Shaw has received research grants and consulting fees from Baxter Healthcare. CR Schermer was an employee of Baxter Healthcare at the time of the study. DN Lobo has received research grants and speaker's honoraria from Baxter Healthcare, B Braun and Fresenius Kabi. SH Munson, V Khangulov and D Hayashida are employees of Boston Strategic Partners, Inc., funded by Baxter Healthcare Corporation to conduct the study analyses. JA Kellum has received research grants and consulting fees from Baxter Healthcare.

## Authors' contributions

ADS was responsible for the design and conduct of the study, data interpretation, preparation, and review and approval of the manuscript. CRS was responsible for the design and conduct of the study, data interpretation, preparation, and review and approval of the manuscript. DNL was responsible for the data interpretation, preparation, and review and approval of the manuscript. SHM was responsible for the design and conduct of the study, data collection, management and analysis, preparation, and review and approval of the manuscript. VK was responsible for the design and conduct of the study, data collection, management and analysis, preparation, and review and approval of the manuscript. DH was responsible for the design and conduct of the study, data collection, management and analysis, preparation, and review and approval of the manuscript. JAK was responsible for the design and conduct of the study, data interpretation, preparation, and review and approval of the manuscript.

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## References

- Awad S, Allison SP, Lobo DN. The history of 0.9 % saline. *Clin Nutr.* 2008;27:179–88.
- Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9 % sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg.* 1999;88:999–1003.
- Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9 % (w/v) saline and 5 % (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. *Clin Sci (Lond).* 2001;101:173–9.
- Veech RL. The toxic impact of parenteral solutions on the metabolism of cells: a hypothesis for physiological parenteral therapy. *Am J Clin Nutr.* 1986;44:519–51.
- Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology.* 1999;90:1265–70.
- Ho AM, Karmakar MK, Contardi LH, Ng SS, Hewson JR. Excessive use of normal saline in managing traumatized patients in shock: a preventable contributor to acidosis. *J Trauma.* 2001;51:173–7.
- Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, et al. 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.* 2001;93:811–6.
- Lobo DN, Stanga Z, Aloysius MM, Wicks C, Nunes QM, Ingram KL, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9 % saline, 4 % succinylated gelatine (Gelofusine) and 6 % hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. *Crit Care Med.* 2010;38:464–70.
- Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond).* 2003;104:17–24.
- Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9 % saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg.* 2012;256:18–24.
- Cotton BA, Guy JS, Morris Jr JA, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock.* 2006;26:115–21.
- Guidet B, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D, et al. A balanced view of balanced solutions. *Crit Care.* 2010;14:325.
- Hansen PB, Jensen BL, Skott O. Chloride regulates afferent arteriolar contraction in response to depolarization. *Hypertension.* 1998;32:1066–70.
- Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest.* 1983;71:726–35.
- McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9 % saline for intra-operative fluid replacement. *Anaesthesia.* 1994;49:779–81.
- O'Malley CM, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9 % NaCl during renal transplantation. *Anesth Analg.* 2005;100:1518–24.
- Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg.* 2001;93:817–22.
- Young JB, Utter GH, Schermer CR, Galante JM, Phan HH, Yang Y, et al. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg.* 2014;259:255–62.
- Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Crit Care Med.* 2002;30:300–5.
- Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. *Chest.* 2006;130:962–7.
- Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest.* 2004;125:243–8.
- Zhou F, Peng ZY, Bishop JV, Cove ME, Singbartl K, Kellum JA. Effects of fluid resuscitation with 0.9 % saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis. *Crit Care Med.* 2014;42:e270–8.
- McCluskey SA, Karkouti K, Wijesundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. *Anesth Analg.* 2013;117:412–21.
- Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9 % saline compared to Plasma-Lyte. *Ann Surg.* 2012;255:821–9.
- Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiwicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med.* 2014;40:1897–905.
- Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. *Crit Care Med.* 2014;42:1585–91.
- Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA.* 2012;308:1566–72.
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22:707–10.
- Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2:1–141.
- Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care.* 1998;36:8–27.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818–29.
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41–55.
- Parsons LS. Performing a 1: N case-control match on propensity score. Proceedings of the 29th Annual SAS® Users Group International Conference; SAS® Institute Inc.; May 9–12 2004; Montreal. (Available at <http://www2.sas.com/proceedings/sugi29/165-29.pdf>).
- Smith CA, Gosselin RC, Utter GH, Galante JM, Young JB, Schermer LA, et al. Does saline resuscitation affect mechanisms of coagulopathy in critically ill trauma patients? An exploratory analysis. *Blood Coagul Fibrinolysis.* 2015;26:250–4.
- Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care.* 2010;14:R185.
- Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med.* 2013;369:2462–3.
- National Clinical Guidance Centre. Intravenous fluid therapy in adults in hospital: Clinical Guideline <CG174>: Methods, evidence and recommendations 2013. Available at <https://www.nice.org.uk/guidance/cg174>. Accessed Sept 8th 2015.

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