PREFERRED CRYSTALLOIDS IN SEPSIS

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22.5.20

Question

- Do low chloride solutions reduce mortality and renal replacement therapy use when compared to high chloride fluids?

TOPICS OF DISCUSSION

- ORIGIN OF CONCEPT
  - BICARBONATE ERA
  - STEWART PRINCIPLE
- BALANCED SOLUTIONS
- ESTABLISHING BENEFITS OF PREFERENTIAL FLUID USE
    - ANIMAL STUDIES
    - CLINICAL TRIALS
    - META ANALYSIS
- COST ANALYSIS

Fluid challenge is cornerstone of hemodynamic resuscitation of septic patients

Administration of 30ml/kg of crystalloids – integral part of “The Severe Sepsis 3-Hour Resuscitation Bundle”

Dellinger *et.al*. 2012 Crit care Med 41(2):580-637, 2013

ORIGIN OF CONCEPT

- THE BICARBONATE ERA - Henderson-Hasselbalch equation for dissociation of carbon dioxide considered bicarbonate as major determinant of acid–base status

$$pH = pK + \log_{10}\left(\frac{[HCO_3^-]}{0.03\ (PaCO_2)}\right)$$

KEY CONCEPTS

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

Principle of mass balance – Alterations in partial pressure of CO2 or levels of hydrogen and bicarbonate affect pH

LIMITATION:

But hydrogen ion concentration is more than million times lower than bicarbonate level indicates other forces at work in regulation of pH

Seifter *et. al.* N Engl J Med 2014;371:1821-31

ORIGIN OF CONCEPT

- THE STEWART APPROACH – Physiochemical approach – integrating the concept of conservation of mass, dissociation of electrolytes and electroneutrality

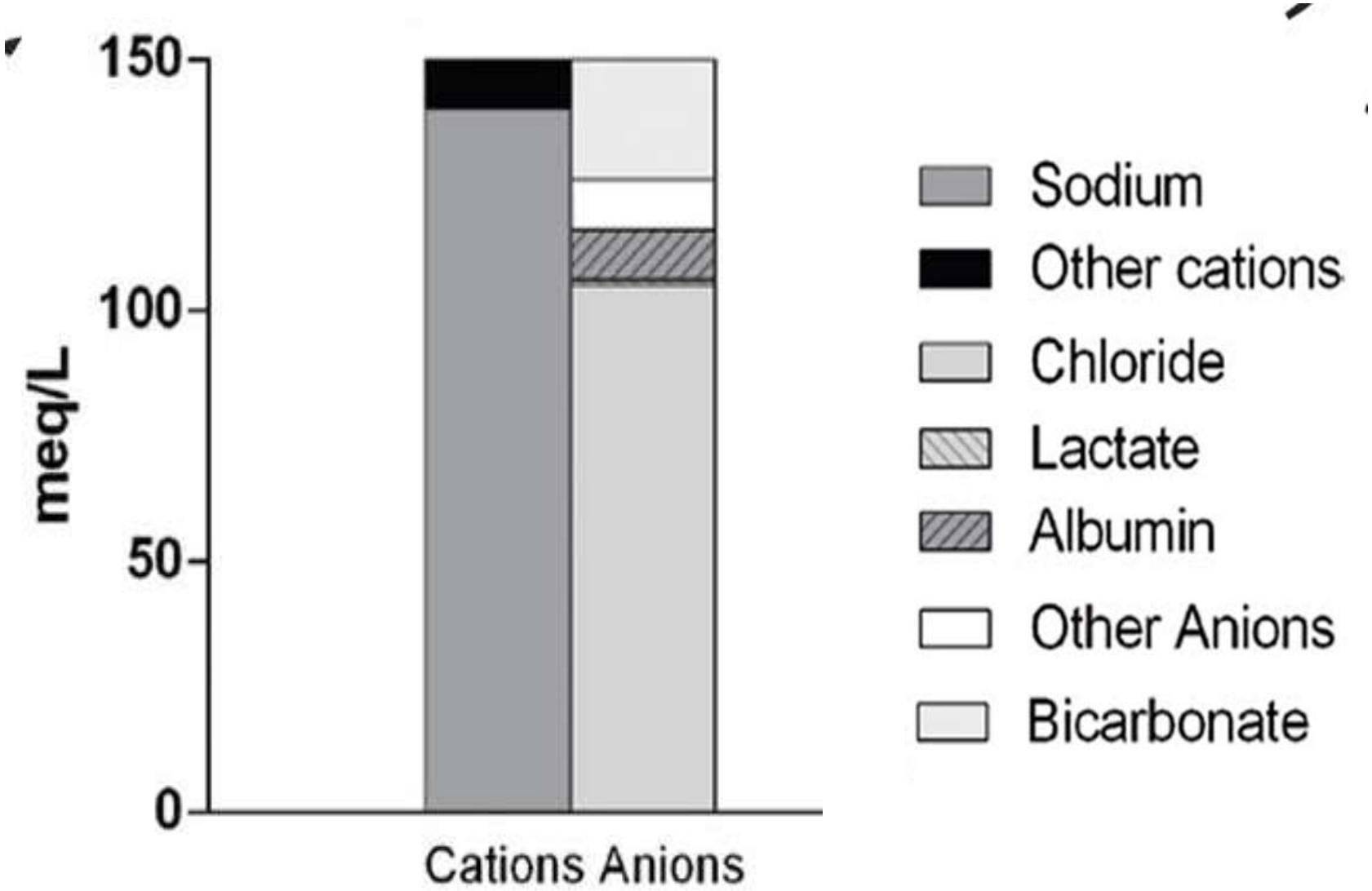
  Law of electroneutrality = All cations and anions must balance

- Plasma pH (and bicarbonate concentration) depends on pCO2, strong ion difference, concentration of weak acids (primarily albumin and phosphate)

Story *et.al*. ANESTHESIA AND ANALGESIA August 2016 Vol 123

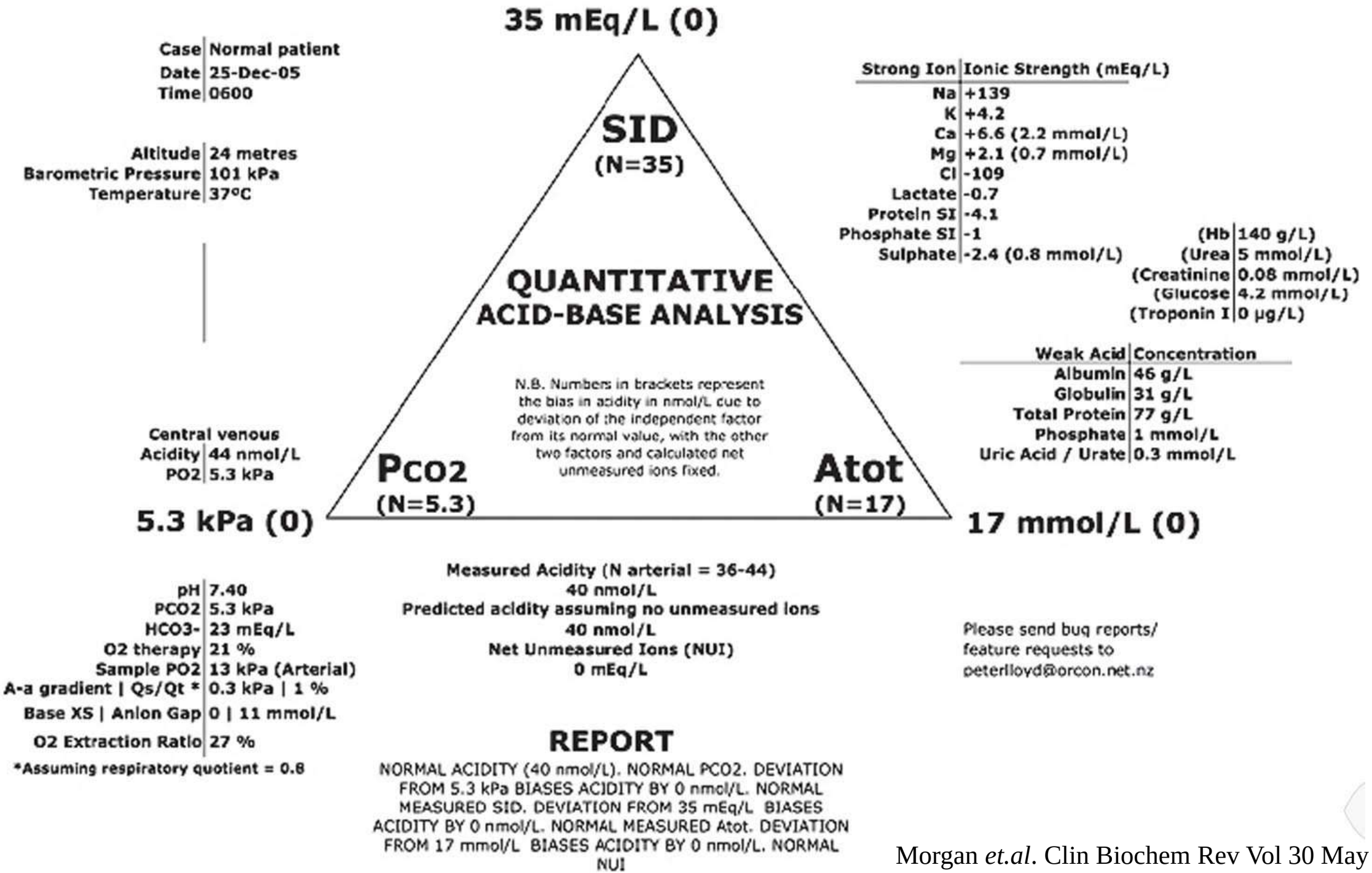
STRONG ION DIFFERENCE

- Strong ions – completely dissociates in solution i.e. plasma
- Measured SID is sum of plasma cations (Na^+, Ca^{2+}, K^+, Mg^{2+}) minus anions (Cl^- and lactate)
- According to concept of electroneutrality, Gamblegram demonstrates ions filling SID between strong cations and anions are primarily bicarbonate (factor dependent on SID) and total amount of weak acids, including albumin (most important weak acid)



GAMBLEGRAM DIAGRAM (Reference values on medians of reference range)

Story *et.al.* ANESTHESIA AND ANALGESIA August 2016 Vol 123

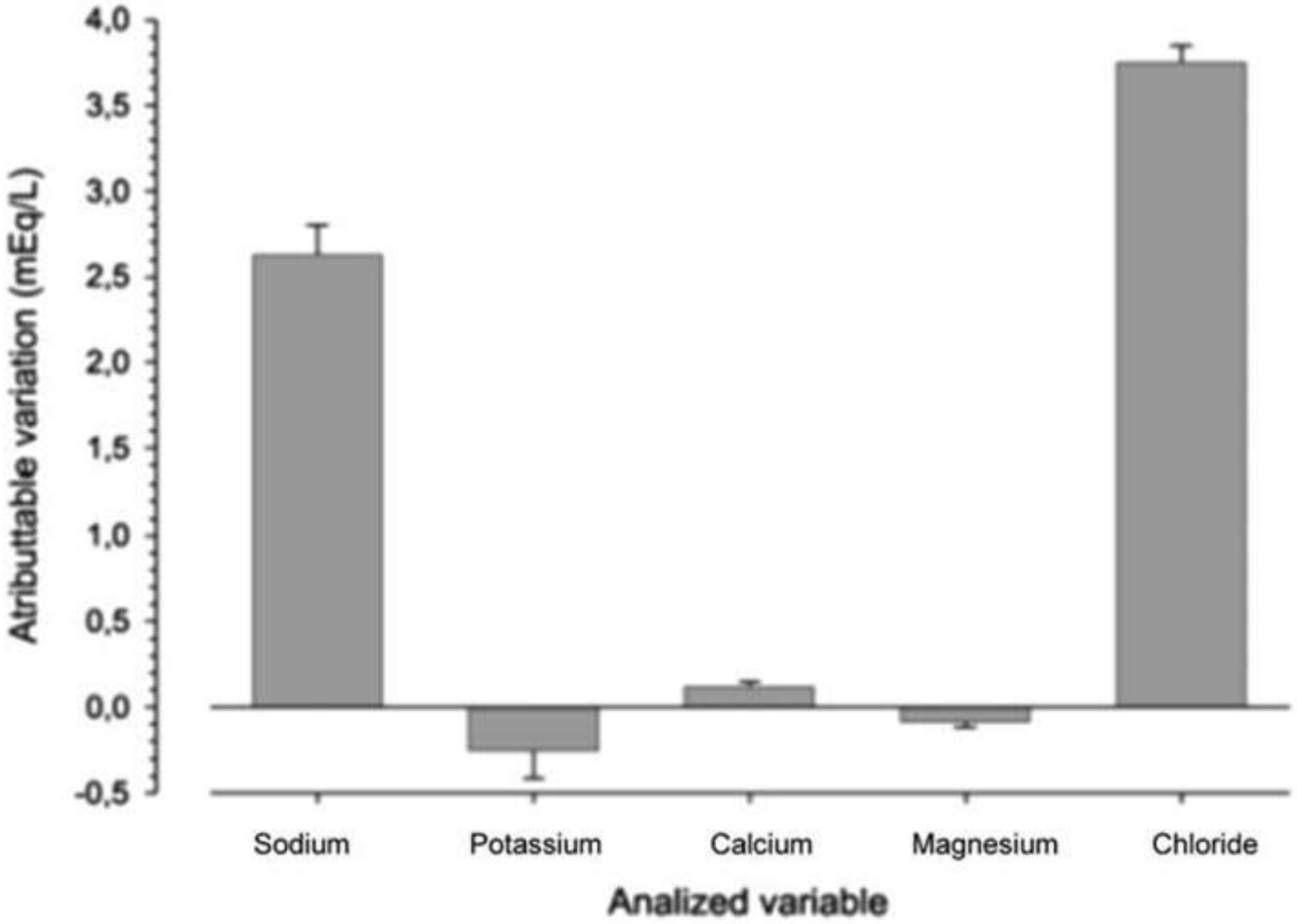


Morgan *et.al*. Clin Biochem Rev Vol 30 May 2009

CLINICAL IMPLICATION

- Normal concentration ratio of sodium to chloride in ECF – 140:100 (approx.)
- Increase in sodium level, decrease in chloride level or both leads to increase in SID and bicarbonate concentration will increase
- Saline induced acidosis develops because infusion of proportionately high Na-Cl containing solution, (ratio < 140:100) will decrease SID and bicarbonate concentration
- Accentuated by insufficient excretion of extra chloride as ammonium chloride leads to metabolic acidosis

Seifter *et. al*. N Engl J Med 2014;371:1821-31



In septic patients, 2 litres of normal saline infusion promptly resulted in elevation of plasma chloride that was disproportionate to sodium concentration. Despite equal concentrations of chloride and sodium in normal saline solution

VARIATION OF PLASMA ELECTROLYTES CONCENTRATION IMMEDIATELY AFTER 2000ml INFUSION OF NORMAL SALINE CONCENTRATION IN SEPTIC PATIENTS

Park et. al. Rev Bras Ter Intensiva 23(2): 176-182, 2011

BASE EXCESS

- Base excess – Amount of strong acid (in millimoles per litre) required to added to fully oxygenated whole blood to return pH of in vitro whole blood to 7.4 at 37°C with $PaCO_2$ held at 40 mm Hg

- Base deficit – negative version of base excess

Modified Stewart approach

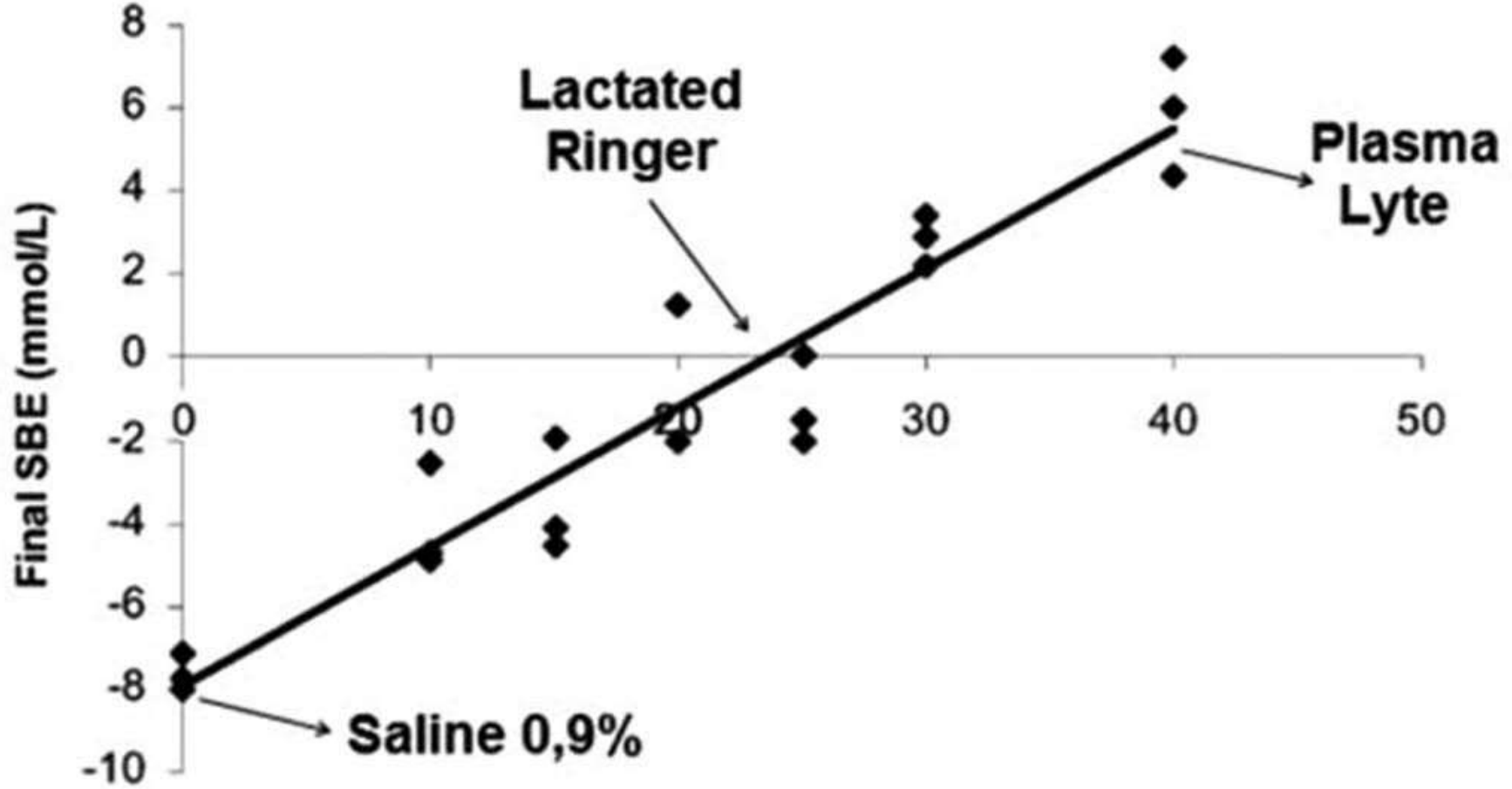
Base excess = [Na-Cl-35] + [1 – lactate] + [0.25 x (42-albumin)] + other ions

Berend *et. al*. N Engl J Med 2018;378:1419-28

BASE EXCESS

- Standard base excess - Calculated value influenced by lactic acidosis, minute ventilation and various therapies, including sodium bicarbonate and intravenous fluids
- Key to use of standard base excess is assessment of metabolic component with negative value less than -6 mmol per liter indicates severe metabolic acidosis

Berend *et. al*. N Engl J Med 2018;378:1419-28



NORMAL SALINE LOAD PROMOTES DISPROPORTIONATE ELEVATION IN PLASMA CHLORIDE CONCENTRATION AS COMPARED TO SODIUM, LEADING TO HYPERCHLOREMIC (LOW STRONG ION DIFFERENCE) METABOLIC ACIDOSIS

Mendes *et.al.* SHOCK Vol. 47 2017

WHY USE OF NORMAL SALINE IS BEING RECONSIDERED??

- Studies demonstrating reduction in renal blood flow velocity and renal cortical tissue perfusion

POSTULATED MECHANISMS:

1. Hyperchloremia with saline inhibits proximal tubular chloride reabsorption, increasing chloride delivery to distal nephron and subsequent negative feedback to renal vessels to limit flow (TUBULOGLOMERULAR feedback)

2. Interstitial edema leads to increase in renal volume and intracapsular pressure

Chowdhury *et.al*. Ann Surg 2012;256:18-24

COMPOSITION OF VARIOUS FLUIDS

	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Lactate	Gluconate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111		1–2		275–295
0.9% saline	154				154				308
Lactated Ringer's	130	4.0	2.7		109		28		273
Plasma-Lyte A®	140	5.0		3.0	98	27		23	294

PLASMA-LYTE 148

- Isotonic, buffered crystalloid solution with physiochemical composition close to human plasma
- Each 1000 ml of PL 148 contains 140 mmol/L sodium, 5 mmol/L potassium, 1.5 mmol/L magnesium, 98 mmol/L chloride, 27 mmol/L acetate and 23 mmol/L of gluconate
- Calcium free so compatible with blood and blood products

Weinberg *et.al.* World J Crit Care Med. 2016 Nov 4; 5(4): 235-250

PLASMA-LYTE 148

- Caloric content – 66 kcal/L
- Numeric 148 is derivative of sum of each cationic concentrations i.e. 140 mEq Na + 5 mEq K and 3 mEq Mg
- pH – 7.4 (Range 6.5-8)
- Supplied in VIAFLEX plastic bag containers – uniquely formulated polyvinyl chloride

Weinberg et.al. World J Crit Care Med. 2016 Nov 4; 5(4): 235-250

PLASMA-LYTE 148

- False positivity to GM antigen because of gluconate
- Osmolality – 271 mOsmol/kg
- Considered as alkalinizing solution with SID 50

Weinberg et.al. World J Crit Care Med. 2016 Nov 4; 5(4): 235-250

EVIDENCE

RANDOMIZED CLINICAL TRIAL

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

Chowdhury *et.al*.

POPULATION: Twenty healthy males

INTERVENTION: Two litres of intravenous infusions over 1hr of 0.9% saline or plasma-Lyte 148 and MRI scan after 90 mins of infusion to measure renal artery blood flow velocity and renal cortical infusion

Chowdhury et.al. Ann Surg 2012;256:18-24

EVIDENCE

RANDOMIZED CLINICAL TRIAL

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 Chowdhury *et.al*.

OUTCOME:

- Sustained hyperchloremia seen with normal saline along with fall in strong ion difference
- Significant reduction in mean renal artery flow velocity and renal cortical tissue perfusion
- Significant increase in extravascular volume with saline

LIMITATION: Despite all these, there was no difference in urinary concentrations of NGAL

Chowdhury et.al. Ann Surg 2012;256:18-24

EVIDENCE

RESEARCH Open Access

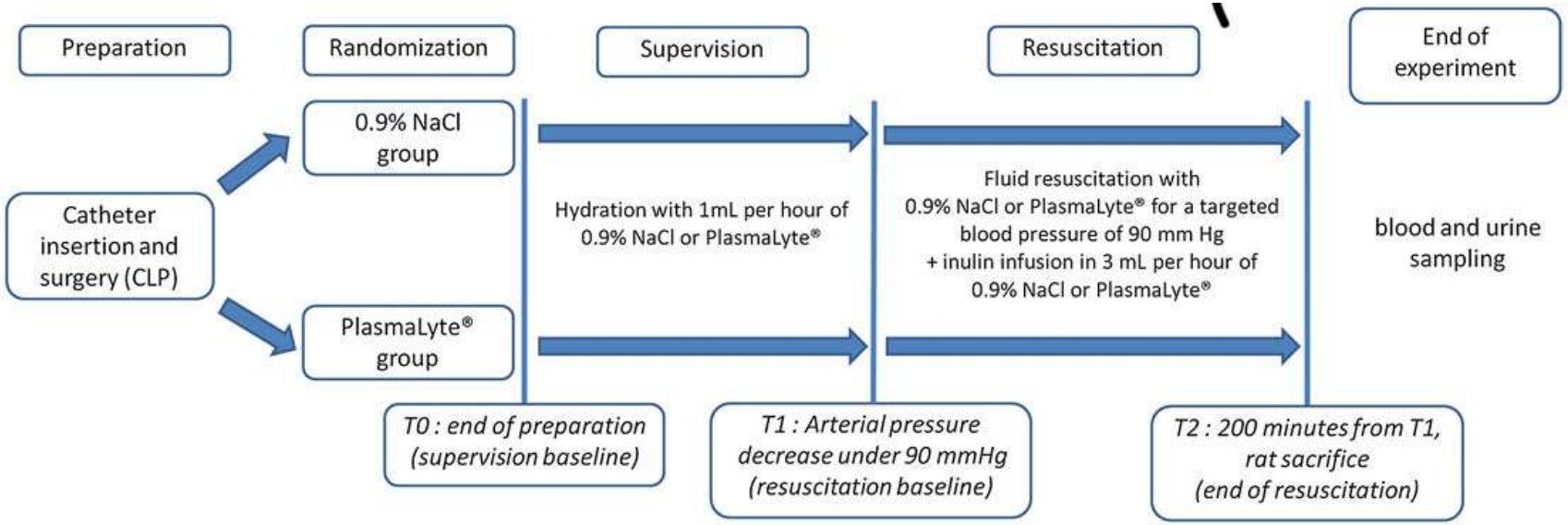
Assessment of renal hemodynamic toxicity of fluid challenge with 0.9% NaCl compared to balanced crystalloid (PlasmaLyte®) in a rat model with severe sepsis

Olivier *et. al.*

Randomized, blind, experimental prospective Trial

POPULATION: Male Winstar rats comparing 0.9% NaCl and Plasmalyte as resuscitation fluid after severe sepsis induced by cecal ligature and puncture

METHODS:



Olivier et al. Ann. Intensive Care (2017) 7:66

EVIDENCE

- **METHODS**:

  - MAP monitored every 10 min until pressure dropped below 90 mm of Hg
  - Monitoring of HR, MAP, pressure in IVC, left carotid and renal arteries blood flow, core temperature and urine output recorded every 10 mins
  - Renal microcirculation measured by velocity in critical capillaries with Side Dark Field Camera movies
  - Renal function measured with inulin and creatinine clearance and RIFLE calculation

- **OUTCOME**: Although incidence of hyperchloremic acidosis was more in saline group but yet both crystalloids had similar effects on systemic and renal hemodynamics

Olivier et al. Ann. Intensive Care (2017) 7:66

EVIDENCE

Effects of Fluid Resuscitation With 0.9% Saline Versus a Balanced Electrolyte Solution on Acute Kidney Injury in a Rat Model of Sepsis' Zhou *et. al.*

POPULATION: Sixty adult male Sprague-Dawley rats

INTERVENTION: Comparison of acute effects of 0.9% saline versus balanced electrolyte solution on acute kidney injury in rat model of sepsis – induced by cecal ligation and puncture

MAIN RESULTS:

- Saline resuscitation resulted in greater chloride levels, significantly decreased pH and base excess
- AKI measured by RIFLE criteria increased with saline resuscitation along with consistent results on kidney histology and biomarkers of AKI
- Urine NGAL were significantly greater in saline resuscitation
- Twenty four hour survival favoured Plasma-Lyte resuscitation

Zhou et al. Crit Care Med. 2014 April

FULLY BALANCED FLUIDS DO NOT IMPROVE MICROVASCULAR OXYGENATION, ACIDOSIS AND RENAL FUNCTION IN A RAT MODEL OF ENDOTOXEMIA Ergin *et. al*.

DESIGN: Randomized study

POPULATION: Five groups of rat were used. Sham group, lipopolysaccharide (LPS) group and 3 LPS groups that received normal saline, bicarbonate buffered crystalloid solution and hydroxyethyl starch ringer solution

INTERVENTION: Systemic hemodynamic variables, renal blood flow, microvascular oxygenation, oxidative/nitrosative stress and renal function

OUTCOME: No difference either between balanced crystalloid (Cl- [119 mmol/L]) and 0.9% NaCl in renal function and renal blood flow

Ergin et al. Shock. 2016;46(1):83-91

Low- Versus High-Chloride Content Intravenous Solutions for Critically Ill and Perioperative Adult Patients: A Systematic Review and Meta-analysis

DOURADO *et. al.*

POPULATION: RCT enrolling critically ill and/or perioperative adult patients

INTERVENTION: Comparison of low to high chloride solution for volume resuscitation or maintainence

OUTCOME: No statistically significant impact on mortality (odds ratio, 1.22; 95% CI- 0.8-1.58)

Underpowered to detect potentially important differences due to small pooled sample size

Studies/Year	Design/Centres	Eligible sample size	Intervention(s) compared to 0.9% saline	Results
Wu *et. al.* 2011	Multicentric/ Critically ill patients:acute pancreatitis	40	Ringer's Lactate NA	Significant reduction in SIRS after 24 hrs among subject resuscitated with lactated ringer's solution (p= .035) Reduction of CRP (51.5 vs 104 mg/dl) (p= 0.02)
Van Zyn *et.al.* 2012	Multicentric/ Critically ill patients: Diabetic ketoacidosis	57	Ringer's Lactate NA	No difference in time to normalization of pH in patients with DKA (p= 0.934) Time to reach blood glucose level to 250mg/dl took longer in ringer's lactate solution (p=0.044)
Young *et.al.* SPLIT Trial	Multicentric, critically ill patients	2262	Plasma-Lyte PL: 2.0 (1.0-3.5) NS: 2.0 (1.0-3.2)	With use of buffered crystalloid compared with saline, there was no reduction in risk of AKI (p=0.91)
Verma *et.al.*	Multi center, critically ill patients	974	Plasma-Lyte PL: 2.9 NS: 3.4	No significant difference in worst BE (p=0.42). No significant difference in AKI (p=0.48), peak creatinine level (p= 0.092) or ICU or hospital mortality

SPLIT TRIAL

- Primary Outcome: In buffered crystalloid solution, 9.6% developed AKI within 90 days as compared to 9.2% in saline group ($p = 0.77$)
- Secondary outcome: No difference in probability of requiring RRT, service utilization, rate of death within 90 days of follow up period

SPLIT TRIAL -LIMITATIONS

- The majority of population was of moderate risk (mean APACHE II – 14) and predominantly included postoperative patients
- Only 4% of population had sepsis
- The incidence of AKI within 90 days of enrollment was approx. 9% and rates of renal replacement therapy and in hospital mortality was approx. 3% and 8% respectively

SPLIT TRIAL -LIMITATIONS

- Although the primary aim of the trail was to assess renal injury, there was no consideration for specific renal markers
- The exposure to fluid was minimal i.e. approximately 2 litres during entire ICU stay
- No correlation between incidence of hyperchloremia and the incidence of AKI

Mortality - IV, Random Effects

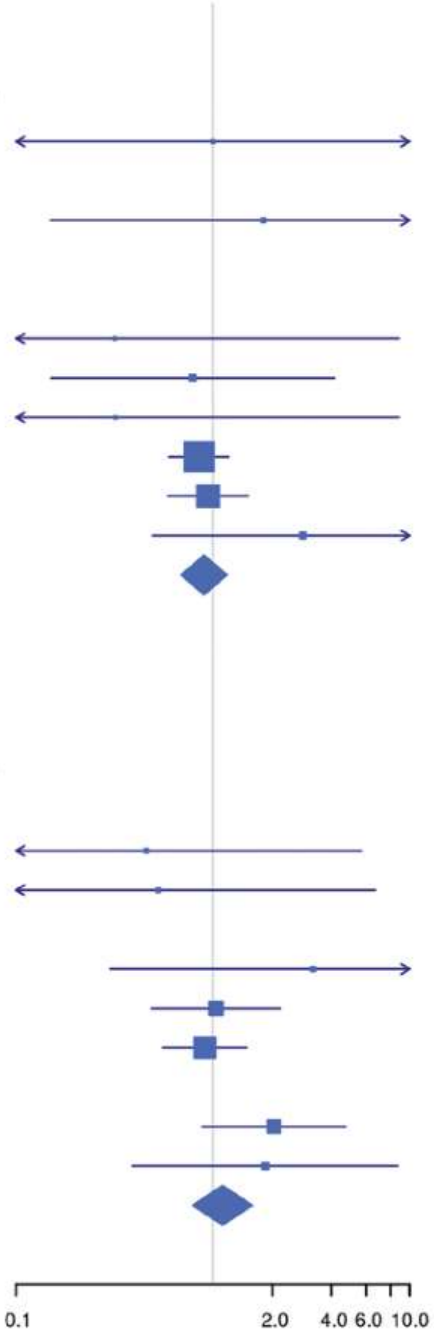
Study	Low Chloride Events	Total	High Chloride Events	Total	OR	95% CI Lower	Upper
Waters 2001	1	33	1	33	1.00	0.06	16.69
Takil 2002	0	15	0	15	NA	NA	NA
Base 2011	2	43	1	38	1.80	0.16	20.73
Wu 2011	0	19	0	21	NA	NA	NA
Van Zyl 2012	0	27	0	27	NA	NA	NA
Volta 2013	0	20	1	20	0.32	0.01	8.26
Young 2014	3	22	4	24	0.79	0.16	4.00
Song 2015	0	25	1	25	0.32	0.01	8.25
Young 2015	87	1152	95	1110	0.85	0.60	1.20
Semler 2016	72	520	68	454	0.95	0.60	1.50
Verma 2016	5	33	2	34	2.86	0.51	15.90
Summary	**170**	**1909**	**173**	**1801**	**0.90**	**0.69**	**1.17**

p = 0.44, I2 = 0%

RRT - IV, Random Effects

Study	Low Chloride Events	Total	High Chloride Events	Total	OR	95% CI Lower	Upper
Takil 2002	0	15	0	15	NA	NA	NA
O Malley 2005	1	26	2	25	0.46	0.04	5.42
Wu 2011	1	19	2	21	0.53	0.04	6.34
Volta 2013	0	20	0	20	NA	NA	NA
Kim 2014	3	30	1	30	3.22	0.32	32.89
Potura 2015	19	74	19	76	1.04	0.50	2.16
Young 2015	38	1152	38	1110	0.91	0.56	1.47
Song 2015	0	25	0	25	NA	NA	NA
Semler 2016	24	520	14	454	2.04	0.90	4.65
Verma 2016	5	33	3	34	1.85	0.40	8.44
Summary	**91**	**1914**	**79**	**1810**	**1.12**	**0.80**	**1.58**

p = 0.518, I2 = 0%



Dourado et al. ANESTHESIA ANALGESIA XXX 2017

CONCLUSIONS

- As per authors, cumulative number of patients considered gave only power of 42% and 23% to detect relative risk reduction of 10% on mortality and RRT respectively
- Fluid exposure was low (median volume approx. 2 lts) so no definitive interpretation can be drawn

CONCLUSIONS

- No difference between low versus high chloride solutions on mortality or RRT in critically ill and perioperative patients
- Chloride level also did not affect AKI (KDIGO ≥ 2) or use of allogenic blood transfusion

Balanced Crystalloids Versus Saline in Critically Ill Adults: A Systematic Review and Meta-analysis

Hammond *et. al.*

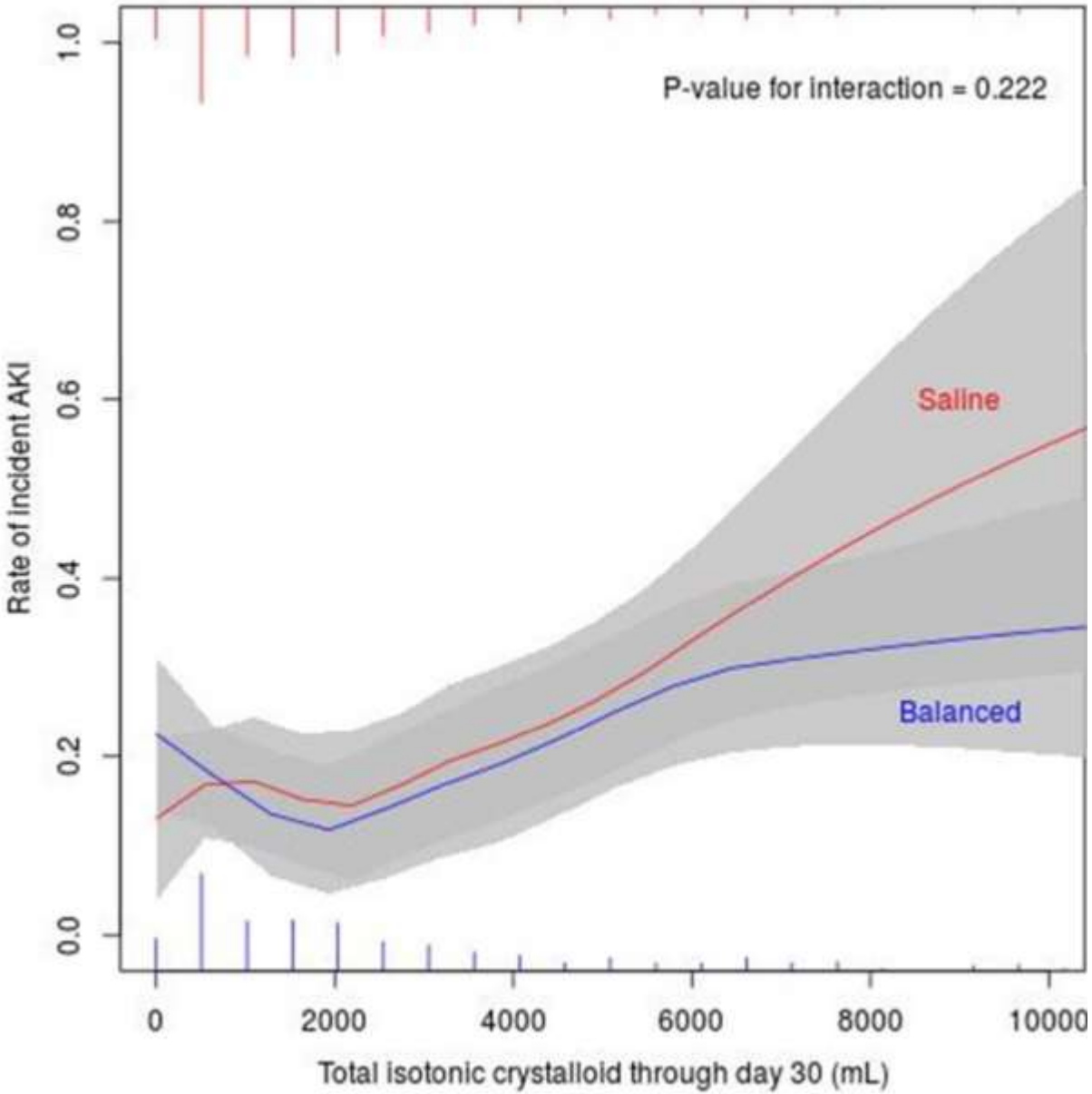
POPULATION: Cohort studies and randomized trials of critically ill nonperioperative patients

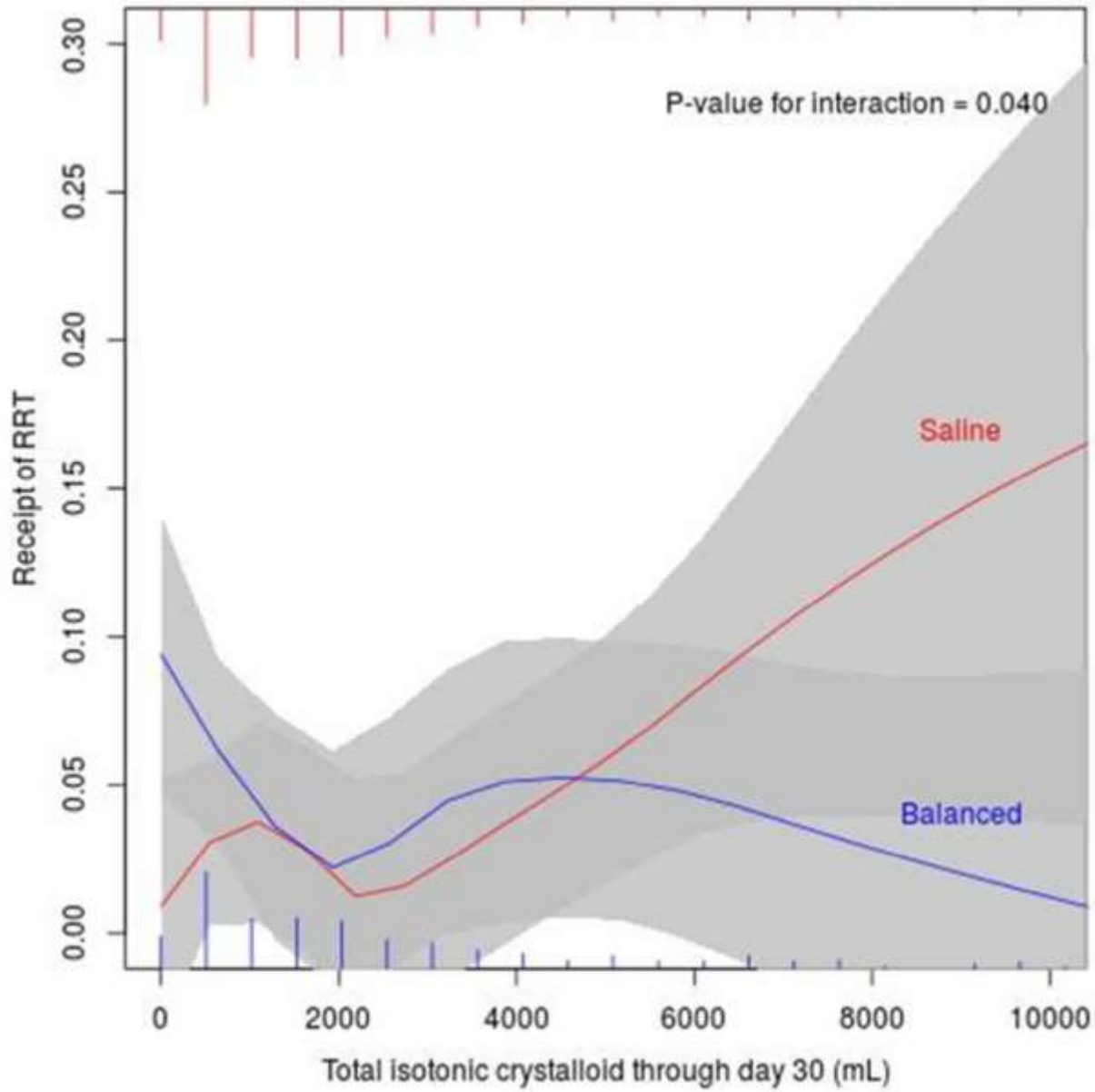
INTERVENTION: Fluid resuscitation with balanced crystalloids or 0.9% sodium chloride (saline)

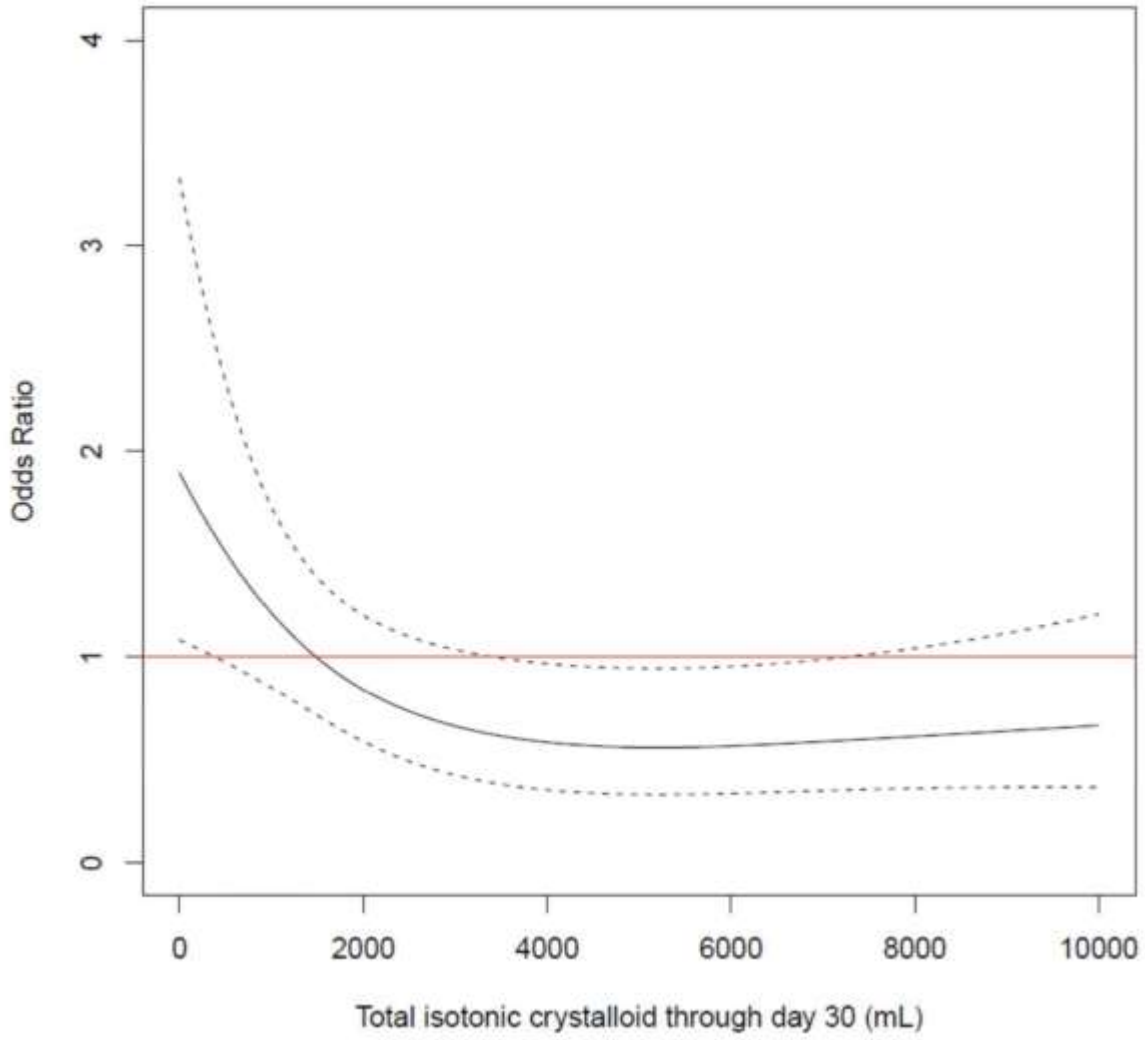
OUTCOME: Balanced crystalloids demonstrated lower hospital or 28-/30- mortality (RR = 0.86; 95% CI = 0.75-0.99)

In sepsis cohort, the incidence of major adverse kidney events occurring in first 30 days were less with balanced crystalloids than saline (OR = 0.78; 95% CI = 0.66-0.91)

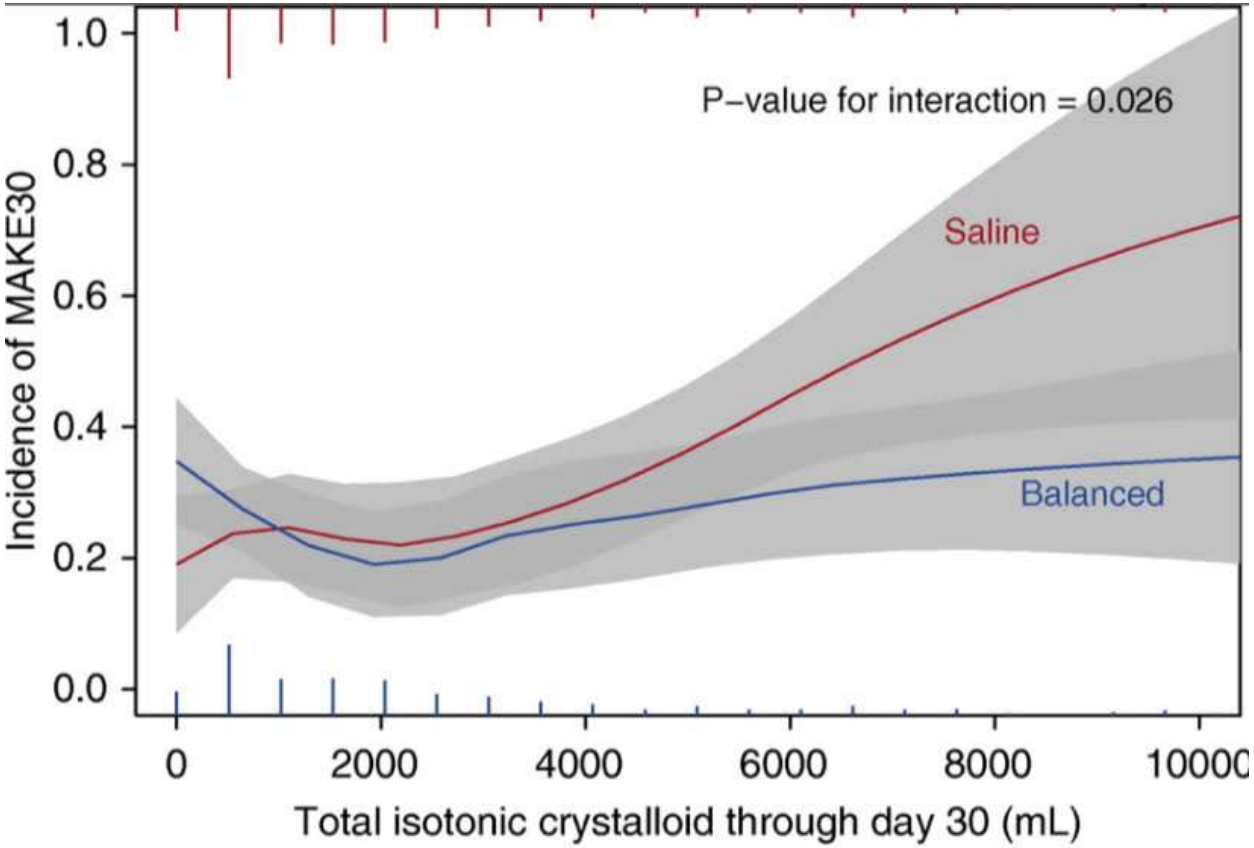
Studies Year	Design/ Centres	Eligible sample size	Intervention(s) compared with 0.9% saline	Results
Raghunathan *et. al*. 2014	Propensity matched cohorts/ 360	6730	Normosol, dextrose 5%, ringer's lactate Balanced solution – Median 7 litres NS – Median 5 litres	Balanced fluids ass. with lower hospital mortality (19.6% vs 22.8%) No significant difference in prevalence of AKI or ICU stay
Shaw et. al. 2015	Propensity matched cohorts	3116	Plasmalyte/normosol Balanced – 3.3 litres NS – 2.8 Litres	Saline ass. with greater in hospital mortality (3.27% vs 1.03%, p <0.001), length of stay (p=0.016), frequency of readmission at 60 and 90 days (p=0.002) and frequency of cardiac, infectious and coagulopathy (p<0.002)
Jaynes *et. al.* 2018	Retrospective/ 57	1107	Balanced crystalloids	AKI higher in patients receiving high chloride fluids (30% vs 21%, p = 0.03)
Semler et. al.	RCT/1	674	Lactated Ringer's, plasmalyte	**DOSE-RESPONSE** relationship Among patients with large volumes of crystalloids, incidence of MAKE30 significantly higher in saline arm p= 0.026

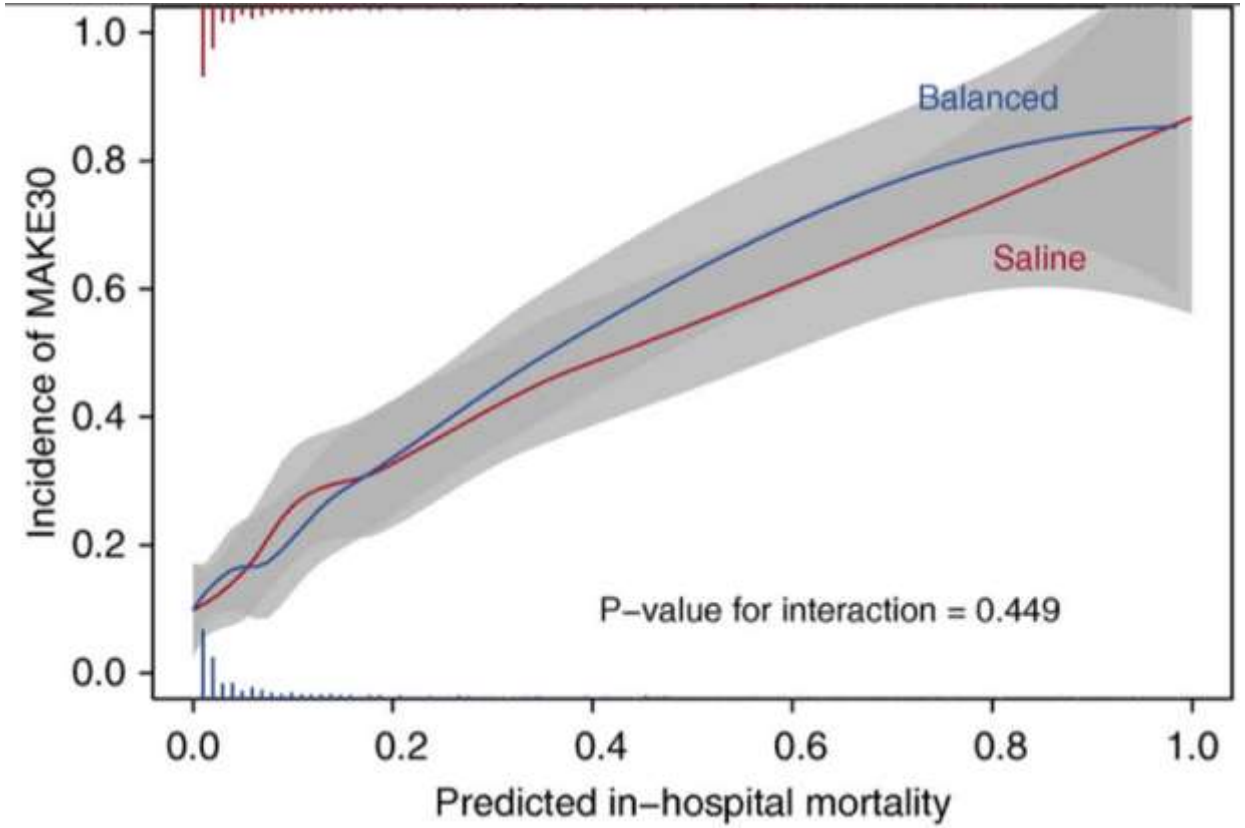

P-value for interaction = 0.222
Saline
Balanced
Rate of incident AKI
0.0
0.2
0.4
0.6
0.8
1.0
0
2000
4000
6000
8000
10000
Total isotonic crystalloid through day 30 (mL)


P-value for interaction = 0.040
Saline
Balanced
Receipt of RRT
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0
2000
4000
6000
8000
10000
Total isotonic crystalloid through day 30 (mL)



The odds of experiencing Major Adverse Kidney Event within 30 days (MAKE30) in balanced crystalloid group compared with saline group relative to total volume of isotonic crystalloid received between enrollment and day 30. Solid black line represents odd ratio for balanced crystalloids compared with saline, dotted black lines represent 95% confidence interval





Major adverse kidney events within 30 days is the presence of any of the following before discharge from hospital or 30 days after enrollment: death, receipt of new renal replacement therapy or final serum creatinine value ≥ 200% of baseline

THE SALT TRIAL Semler et al. Am J Respir Crit Care Med Vol 195

ASSOCIATION BETWEEN CHLORIDE CONTENT OF INTRAVENOUS FLUIDS AND ACUTE KIDNEY INJURY IN CRITICALLY ILL MEDICAL PATIENTS WITH SEPSIS Jaynes *et. al.*

SINGLE CENTRE, RETROSPECTIVE COHORT STUDY

COHORT: 410 patients of severe sepsis and septic shock

(209 in high chloride and 201 in low chloride group)

Exclusion criteria included patients receiving less than 2 litres of fluids at initial resuscitation and length of hospital stay less than 3 days

INTERVENTION: During acute resuscitation period, high chloride (0.9% NaCl) and low chloride (Ringer's lactate and electrolyte –A) fluids

ASSOCIATION BETWEEN CHLORIDE CONTENT OF INTRAVENOUS FLUIDS AND ACUTE KIDNEY INJURY IN CRITICALLY ILL MEDICAL PATIENTS WITH SEPSIS Jaynes *et. al.*

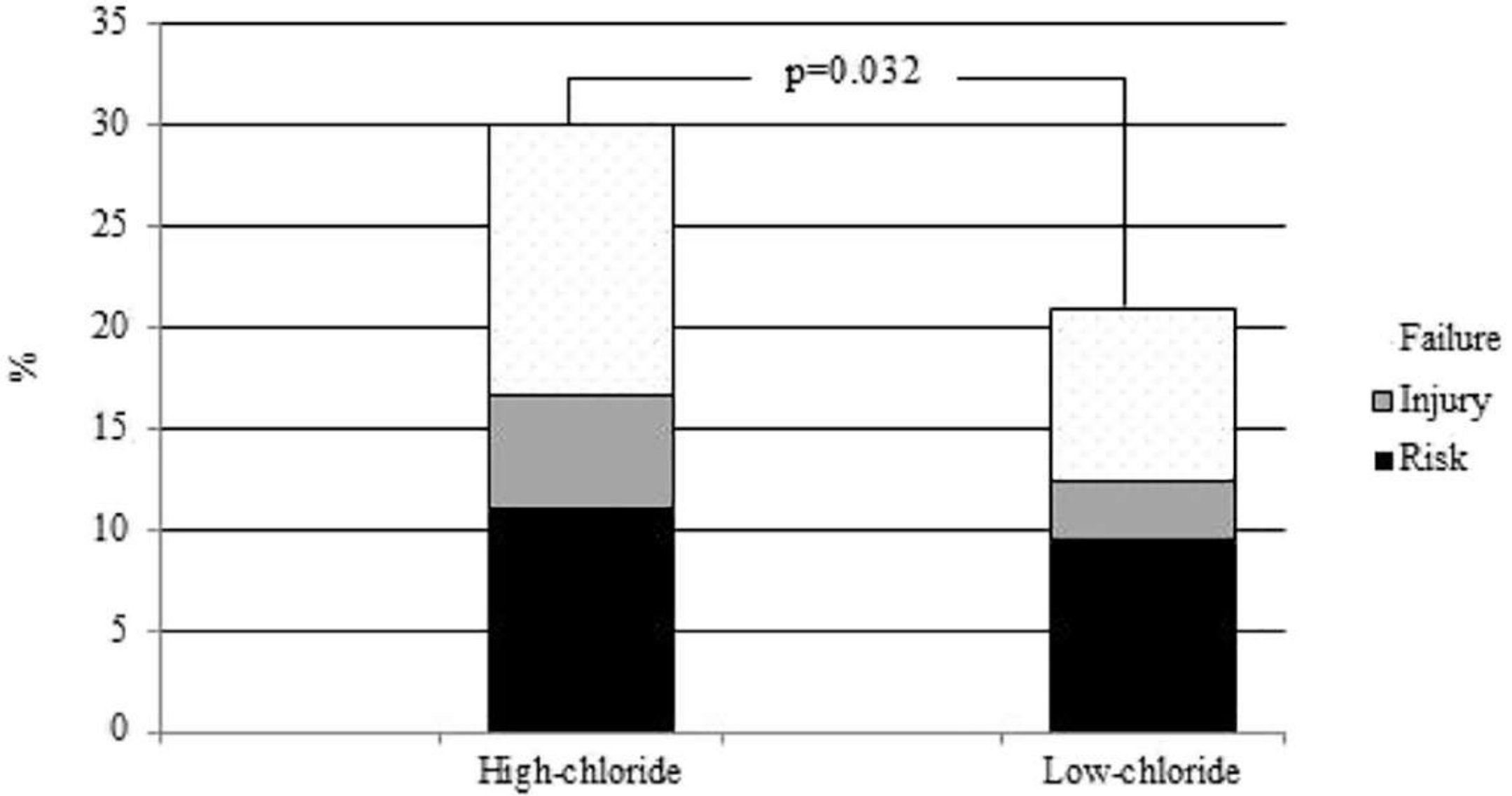
OUTCOME: Patient in high chloride group showed greater change in serum chloride from baseline compared to low chloride solution (p=0.001) and higher incidence of hyperchloremic non-gap metabolic acidosis (50 vs 37%, p = 0.07)

Greater incidence of AKI in high chloride group as compared to low chloride group (30% vs 21%, p = 0.03)

	High-Chloride (n=209)	Low-Chloride (n=201)	p-value
Age, years	58 ± 14.7	61 ± 14.1	0.03
Male, n (%)	103 (51.2)	117 (56)	0.34
Height, cm	170 [163-178]	170 [163-178]	0.99
Weight, kg	79 [66-103]	19 [64-102]	0.47
Admission, n (%) ED Floor	 109 (52.2) 100 (47.8)	 93 (46.3) 108 (53.7)	0.23
ICU Admit Indication, n (%) Hemodynamic instability Respiratory Neurologic Gastrointestinal Metabolic Renal	 91 (43.5) 90 (43.1) 15 (7.2) 2 (1) 10 (4.8) 1 (0.5)	 94 (46.8) 91 (45.3) 12 (6) 3 (1.5) 2 (1) 1 (0.5)	0.25
Severe Sepsis, n (%) Septic Shock, n (%)	92 (44) 117 (56)	60 (29.9) 141 (70.1)	0.003
Diabetes, n (%)	51 (24.4)	46 (22.9)	0.73
Congestive heart failure, n (%)	31 (14.8)	32 (15.9)	0.79
Mild liver disease, n (%) Moderate- severe liver disease, n (%)	9 (4.3) 1 (0.5)	9 (4.5) 2 (1)	0.93 0.62
Chronic kidney disease, n (%)	19 (9.1)	31 (15.4)	0.05
Charlson Comorbidity Index score	3 [2-5]	3 [1-5]	0.3
APACHE II score	17.3 ± 5.9	16.7 ± 6.1	0.32
Baseline SCr, mmol/L	1.2 [0.8-1.9]	1.2 [0.8-2]	0.65
Baseline pH	7.3 ± 0.1	7.38 ± 0.11	0.17
Baseline bicarbonate, mmol/L	23.3 ± 5.4	24.2 ± 7.3	0.8
Baseline chloride, mg/dl	101 [97-107]	104 [100-108]	0.0001

Jaynes et al. j.jcrc.2017.12.014

	High-Chloride (n=209)	Low-Chloride (n=201)	p-value
Total fluids,ml	6500 [4550-12000]	6750 [4013-10000]	0.58
0.9% NaCl, ml	5700 [4000-8061]	1000 [0-2000]	
% NaCl	100 [79-100]	13.3 [0-27]	
Lactated ringers, ml	0 [0-1000]	4200 [3000-7450]	
% Lactated ringers	0 [0-17]	74.5 [57-100]	
Electrolyte-A, ml	0 [0]	0 [0-2000]	
% Electrolyte-A	0 [0]	0 [0-25]	
% Total balanced fluids	0 [0-20]	86.7 [73-100]	
Total chloride, mEq	979 [664-1386]	785 [486-1153]	

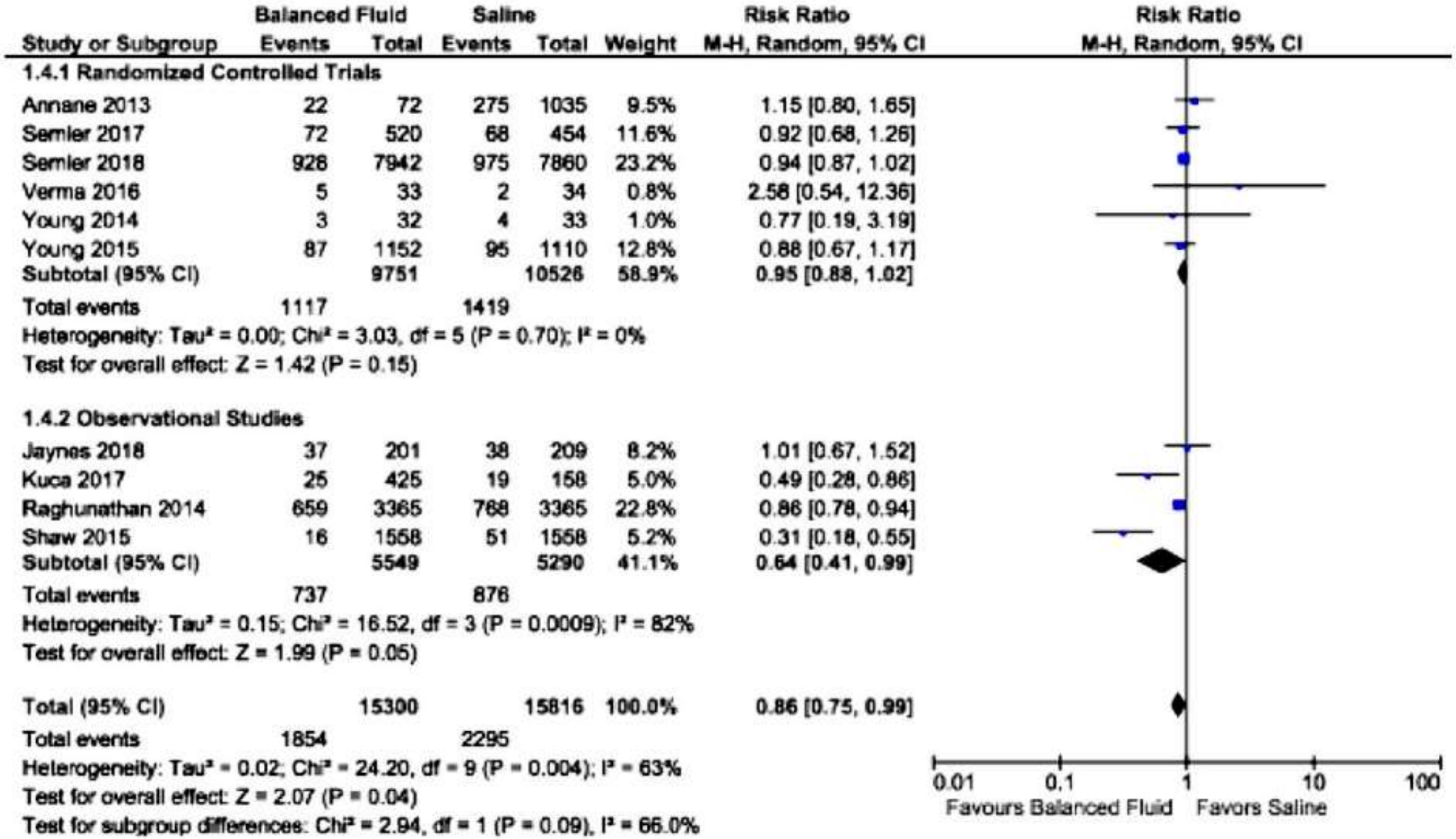


Jaynes et al. j.jcrc.2017.12.014

LIMITATIONS

- Retrospective, single centre cohort

- No data regarding amount of fluid received prior to registration in the study



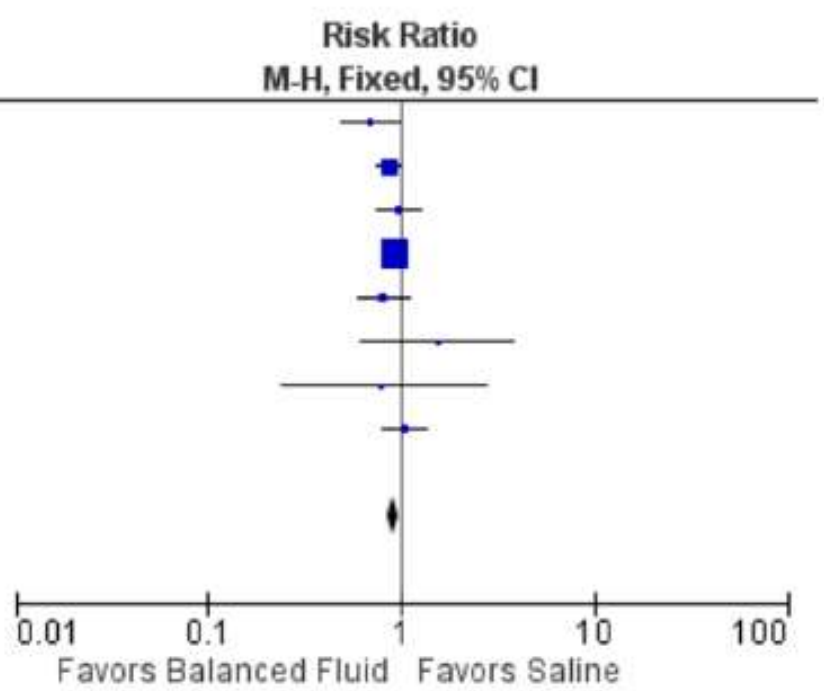
HOSPITAL AND 28/30 DAY MORTALITY OVERALL

Hammond et al. Annals of Pharmacotherapy I-9

Study or Subgroup	Balanced Fluid Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jaynes 2018	42	201	63	209	4.0%	0.69 [0.49, 0.97]
Raghunathan 2014	301	3365	348	3365	22.4%	0.86 [0.75, 1.00]
Semler 2017	97	520	87	454	6.0%	0.97 [0.75, 1.26]
Semler 2018	807	7942	858	7860	55.4%	0.93 [0.85, 1.02]
Shaw 2015	69	1558	85	1558	5.5%	0.81 [0.60, 1.11]
Verma 2016	9	32	6	33	0.4%	1.55 [0.62, 3.85]
Waters 2001	4	33	5	33	0.3%	0.80 [0.24, 2.72]
Young 2015	102	1067	94	1025	6.2%	1.04 [0.80, 1.36]
Total (95% CI)		**14718**		**14537**	**100.0%**	**0.91 [0.85, 0.98]**
Total events	1431		1546			

Heterogeneity: Chi² = 6.29, df = 7 (P = 0.51); I² = 0%

Test for overall effect: Z = 2.68 (P = 0.007)



PROGRESSION TO RENAL REPLACEMENT THERAPY

CONCLUSION

- From the meta analysis, average increase in serum chloride- 7.4 mEq/L higher with saline than balanced crystalloids
- In sepsis cohort, odds of MAKE30 were less with balanced crystalloids than saline (OR = 0.78, 95% CI = 0.66-0.91) but the same results were not reproduced for mortality

LIMITATIONS

- Fluid volume was not assessed across all studies, so cannot establish the study outcome with respect of fluid volume
- Effect of medication diluents responsible for cumulative volume and hyperchloremia in critically ill patients

SMART Trial

- Cluster randomized, multiple-crossover, unblinded trial
- Conducted in 5 ICUs at Vanderbilt University at Nashville
- Cohort – 15,802 adults to receive saline (0.9% NaCl) or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A)

Semler et.al. N Engl J Med 2018; 378:829-39

SMART TRIAL

PRIMARY OUTCOME –

- Death from any cause before the earlier of hospital discharge or 30 days after ICU admission (30 days in-hospital mortality)

Additional clinical outcomes included:

- Sixty days in-hospital mortality and ICU-free days, ventilator–free days, renal replacement therapy free days during 28 days after ICU admission

Semler et.al. N Engl J Med 2018; 378:829-39

SMART Trial

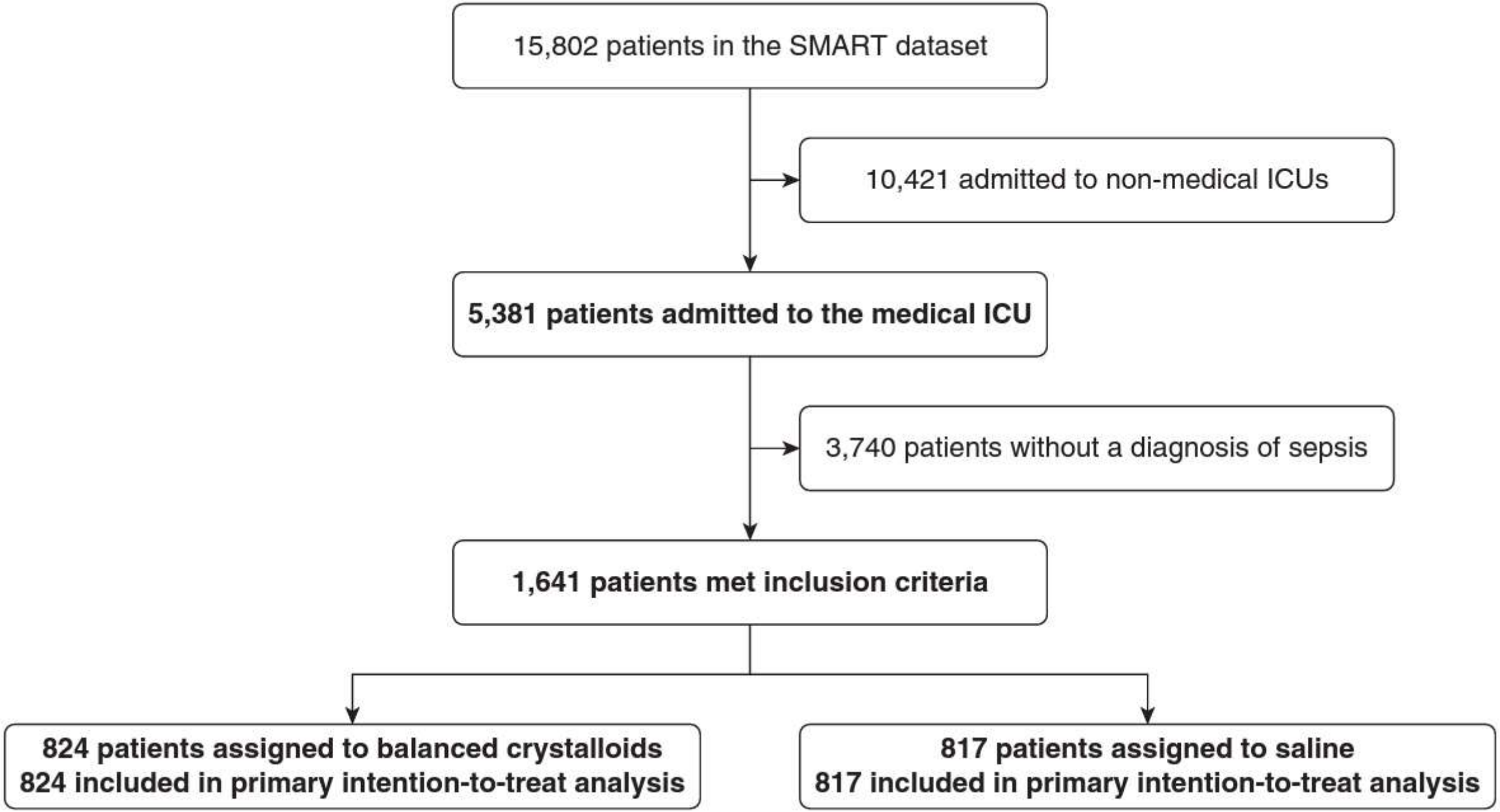
- Additional renal outcomes

1. Proportion of patients with major adverse kidney event within 30 days (MAKE-30) defined as death, new receipt of renal replacement therapy, or persistent renal dysfunction at first of hospital discharge or 30 days

2. New receipt of renal replacement therapy; persistent renal dysfunction (final inpatient creatinine concentration ≥ 200% of baseline) and stage 2 or greater AKI by KDIGO

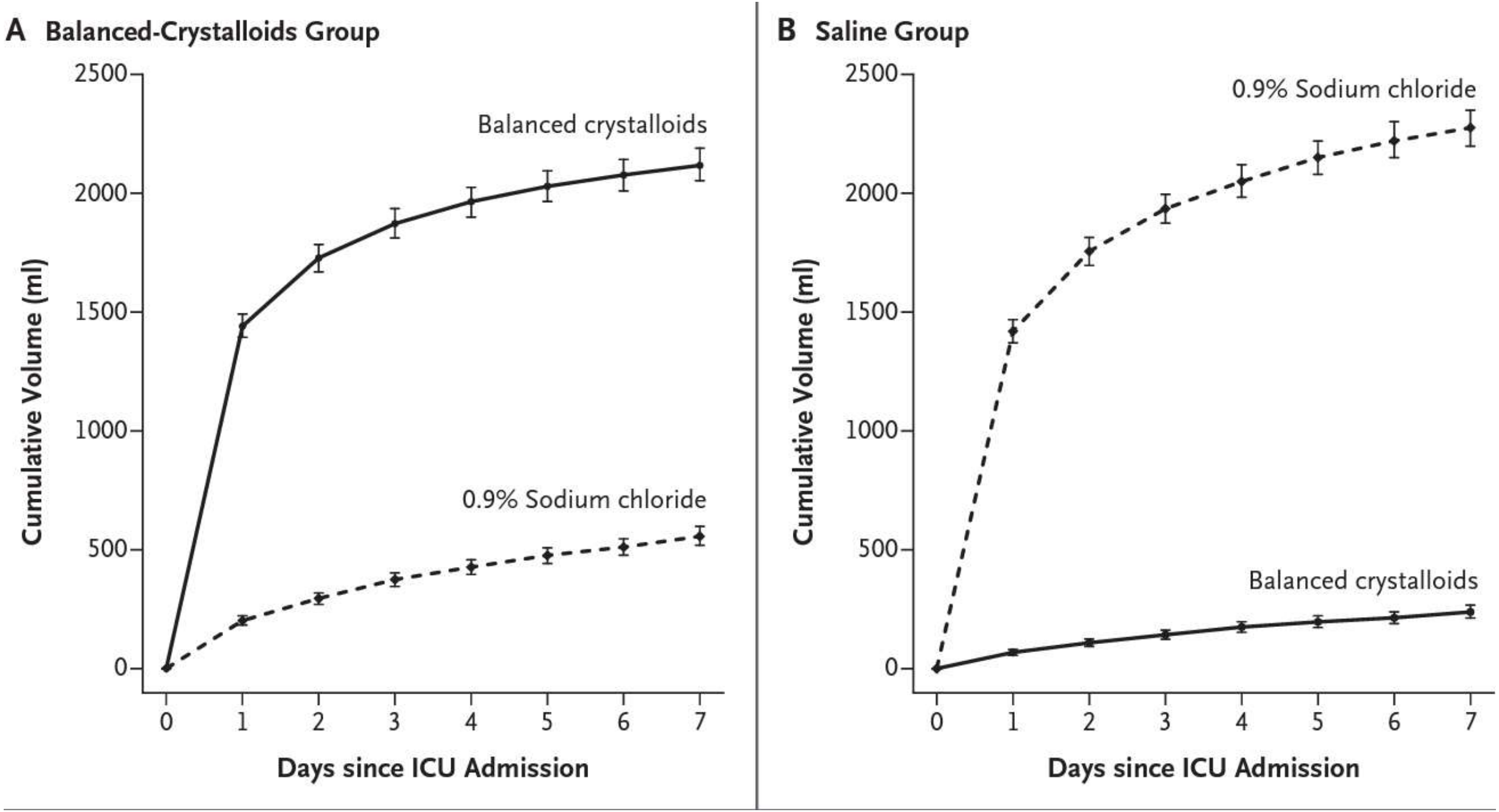
Additional exploratory outcomes include mean arterial pressure, vasopressor receipt and dose and plasma lactate concentration

Semler et.al. N Engl J Med 2018; 378:829-39


15,802 patients in the SMART dataset
10,421 admitted to non-medical ICUs
5,381 patients admitted to the medical ICU
3,740 patients without a diagnosis of sepsis
1,641 patients met inclusion criteria
824 patients assigned to balanced crystalloids
824 included in primary intention-to-treat analysis
817 patients assigned to saline
817 included in primary intention-to-treat analysis

BASELINE CHARACTERISTICS

Patient Characteristics*	Balanced Crystalloids (*n* = 824)	Saline (*n* = 817)
Age, yr	60 (48–69)	60 (47–69)
Men, *n* (%)	451 (54.7)	448 (54.8)
White, *n* (%)	617 (74.9)	618 (75.6)
Weight, kg†	78 (64–98)	77 (64–94)
Chronic comorbidities, *n* (%)‡		
Pulmonary	204 (24.8)	214 (26.2)
Chronic heart failure	200 (24.3)	184 (22.5)
Chronic liver disease	177 (21.5)	198 (24.2)
Diabetes	310 (37.6)	279 (34.1)
Drug abuse	38 (4.6)	58 (7.1)
Metastatic malignancy	78 (9.5)	82 (10.0)
AIDS	20 (2.4)	21 (2.6)
Renal		
Chronic kidney disease, stage III or greater§	169 (20.5)	157 (19.2)
Prior renal replacement therapy receipt	91 (11.0)	92 (11.3)
Source of admission to the ICU, *n* (%)		
Emergency department	464 (56.3)	458 (56.1)
Transfer from another hospital	179 (21.7)	180 (22.0)
Hospital ward	154 (18.7)	159 (19.5)
Operating room	15 (1.8)	8 (1.0)
Another ICU within the hospital	9 (1.1)	10 (1.2)
Outpatient	3 (0.4)	2 (0.2)
Sepsis as primary diagnosis at ICU admission, *n* (%)‖	577 (70.0)	573 (70.1)
Suspected source of infection, *n* (%)‖		
Pulmonary	189 (32.8)	164 (28.6)
Urinary	97 (16.8)	94 (16.4)
Intraabdominal	78 (13.5)	83 (14.5)
Skin and soft tissue	35 (6.1)	36 (6.3)
Bloodstream	22 (3.8)	28 (4.9)
Other	43 (7.4)	51 (8.9)
Multiple sources suspected	83 (14.4)	87 (15.2)
No confirmed source	30 (5.2)	30 (5.2)
Vasopressors, *n* (%)	289 (35.1)	270 (33.0)
Vasopressor dose, norepinephrine equivalent, μg/kg/min¶	0.11 ± 0.27	0.11 ± 0.30
Mean arterial pressure, mm Hg	73 (62–87)	74 (63–88)
Mechanical ventilation, *n* (%)	324 (39.3)	333 (40.8)
SOFA score**	7 (5–10)	8 (5–11)
White blood cell count, $10^3/\mu l$††	13.9 (8.3–19.9)	12.7 (8.3–19.0)
Platelet count, $10^3/\mu l$††	189 (116–284)	189 (107–280)
Hb, g/dl††	10.4 (8.7–12.2)	10.2 (8/7–12.3)
Baseline creatinine, mg/dl‡‡	0.88 (0.67–1.21)	0.87 (0.66–1.23)
Acute kidney injury, stage II or greater§§	207 (25.1)	208 (25.4)



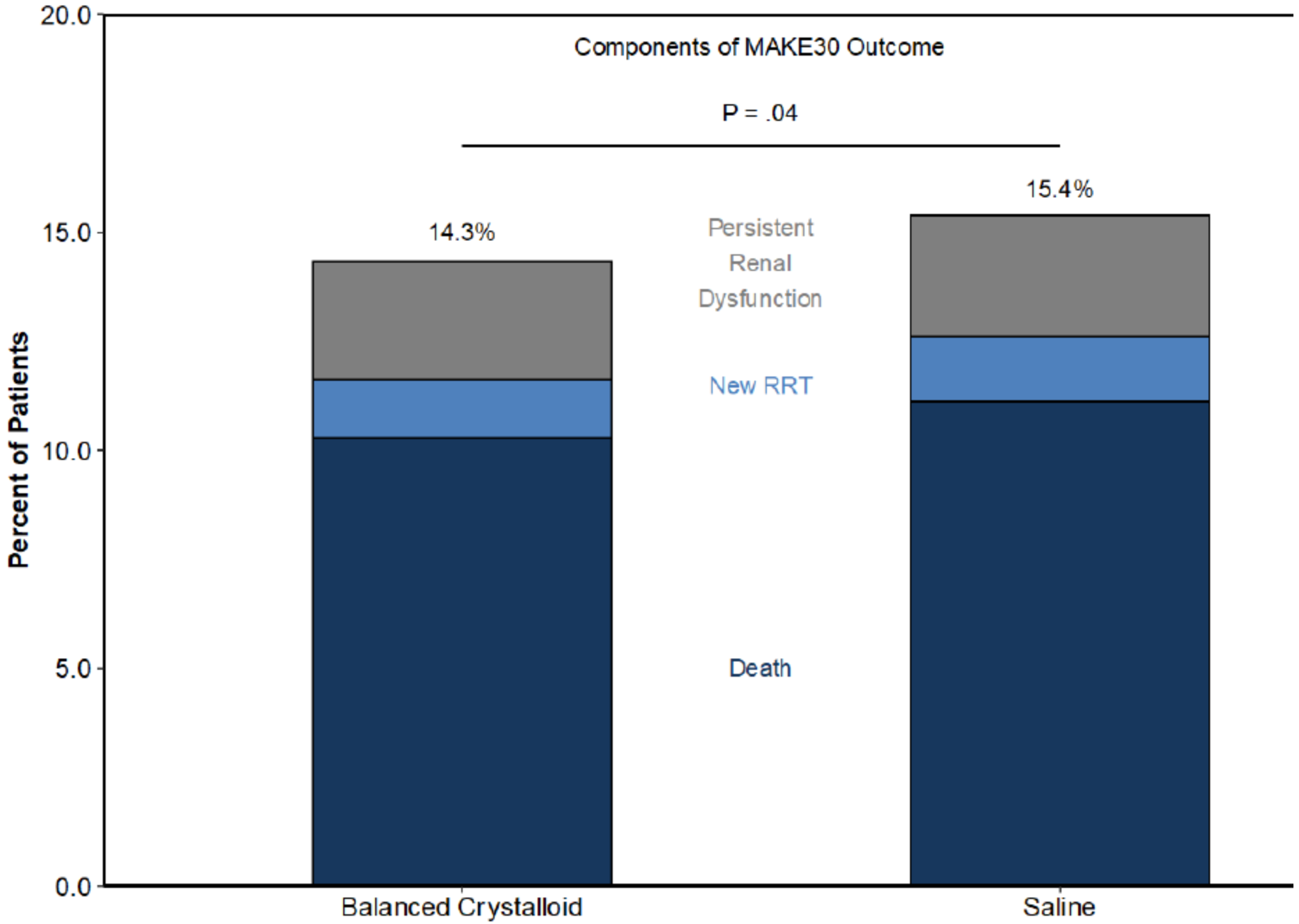
Semler et.al. N Engl J Med 2018; 378:829

SMART Trial

- In prespecified subgroup analysis, effect of balanced crystalloids compared with saline on composite outcome appeared to be greater among patients with sepsis (odds ratio [OR], 0.8; 95% confidence interval 0.67-0.94)
- Although this difference did not achieve statistical significance (p = 0.06)

Semler et.al. N Engl J Med 2018; 378:829-39

Outcome*	n	Balanced Crystalloids (n = 824)	Saline (n = 817)	Adjusted OR (95% CI)†
Primary outcome				
30-d in-hospital mortality, n (%)	1,641	217 (26.3)	255 (31.2)	0.74 (0.59 to 0.93)
Additional clinical outcomes				
60-d in-hospital mortality, n (%)	1,641	241 (29.2)	269 (32.9)	0.80 (0.64 to 1.01)
ICU-free days‡, median (IQR)	1,641	23 (0 to 26)	23 (0 to 26)	1.15 (0.97 to 1.38)
Mean ± SD	—	17 ± 11	16 ± 12	—
Ventilator-free days‡, median (IQR)	1,641	27 (0 to 28)	26 (0 to 28)	1.37 (1.12 to 1.68)
Mean ± SD	—	19 ± 12	18 ± 13	—
Vasopressor-free days‡, median (IQR)	1,641	27 (0 to 28)	27 (0 to 28)	1.25 (1.02 to 1.54)
Mean ± SD	—	20 ± 12	19 ± 13	—
Renal replacement therapy–free days‡, median (IQR)	1,641	28 (0 to 28)	28 (0 to 28)	1.35 (1.08 to 1.69)
Mean ± SD	—	20 ± 12	19 ± 13	—
Additional renal outcomes§				
Major adverse kidney event within 30 d, n (%)‖	1,641	292 (35.4)	328 (40.1)	0.78 (0.63 to 0.97)
Receipt of new renal replacement therapy, n (%)§	1,458	54 (7.4)	75 (10.3)	0.71 (0.48 to 1.04)
Final creatinine ⩾200% of baseline, n (%)	1,458	164 (22.4)	162 (22.3)	0.99 (0.76 to 1.28)
Stage II or greater AKI developing after ICU admission, n (%)¶	1,458	201 (27.4)	231 (31.9)	0.79 (0.63 to 1.00)
Creatinine**, mg/dl	1,458			
Highest before discharge or 30 d	—	1.58 (0.87 to 3.00)	1.59 (0.93 to 2.97)	0.95 (0.79 to 1.13)
Change from baseline to highest value	—	0.18 (−0.07 to 1.13)	0.23 (−0.07 to 1.20)	0.99 (0.82 to 1.18)
Final value before discharge or 30 d	—	0.94 (0.69 to 1.77)	0.95 (0.71 to 1.80)	0.97 (0.81 to 1.16)



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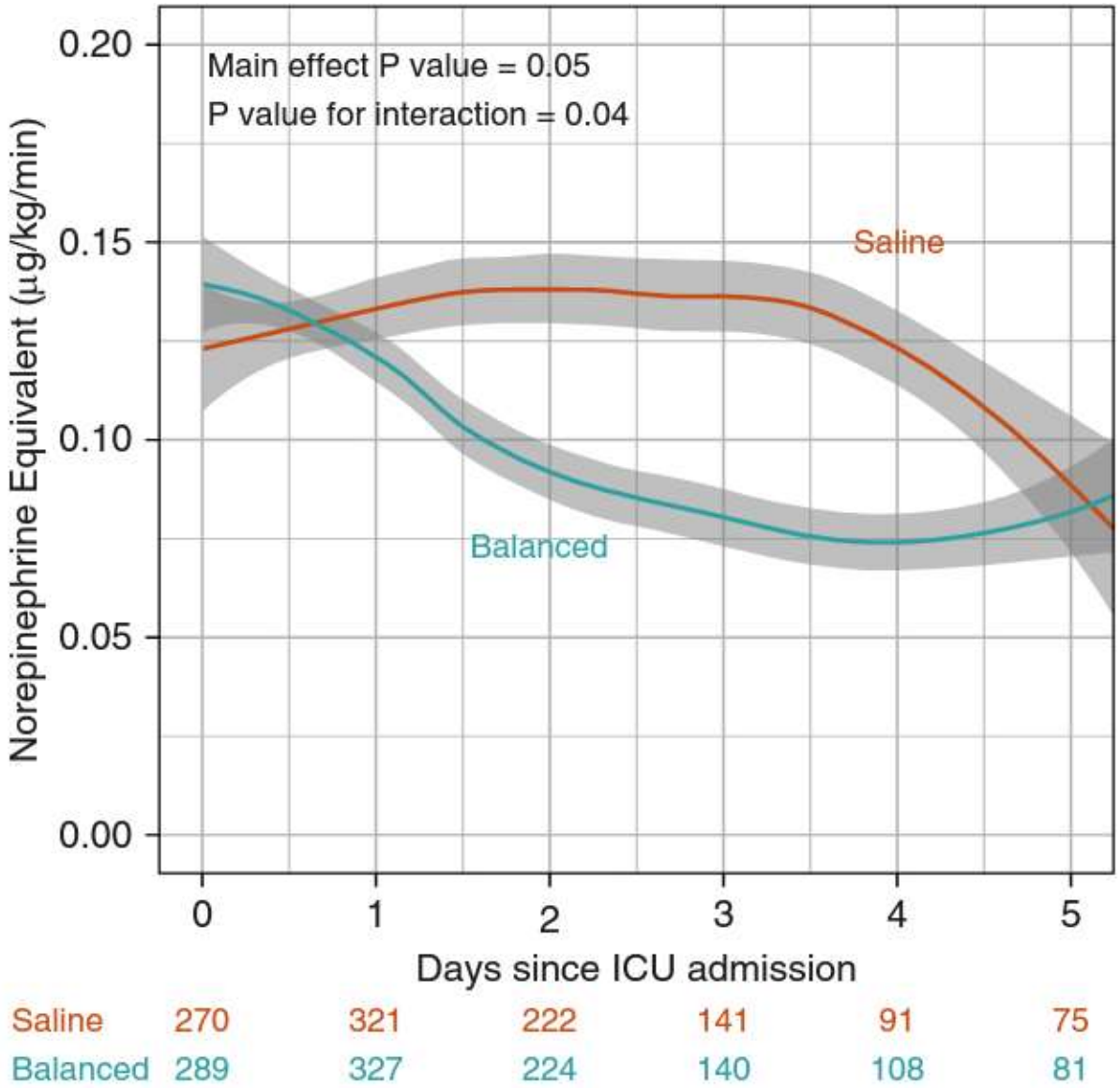

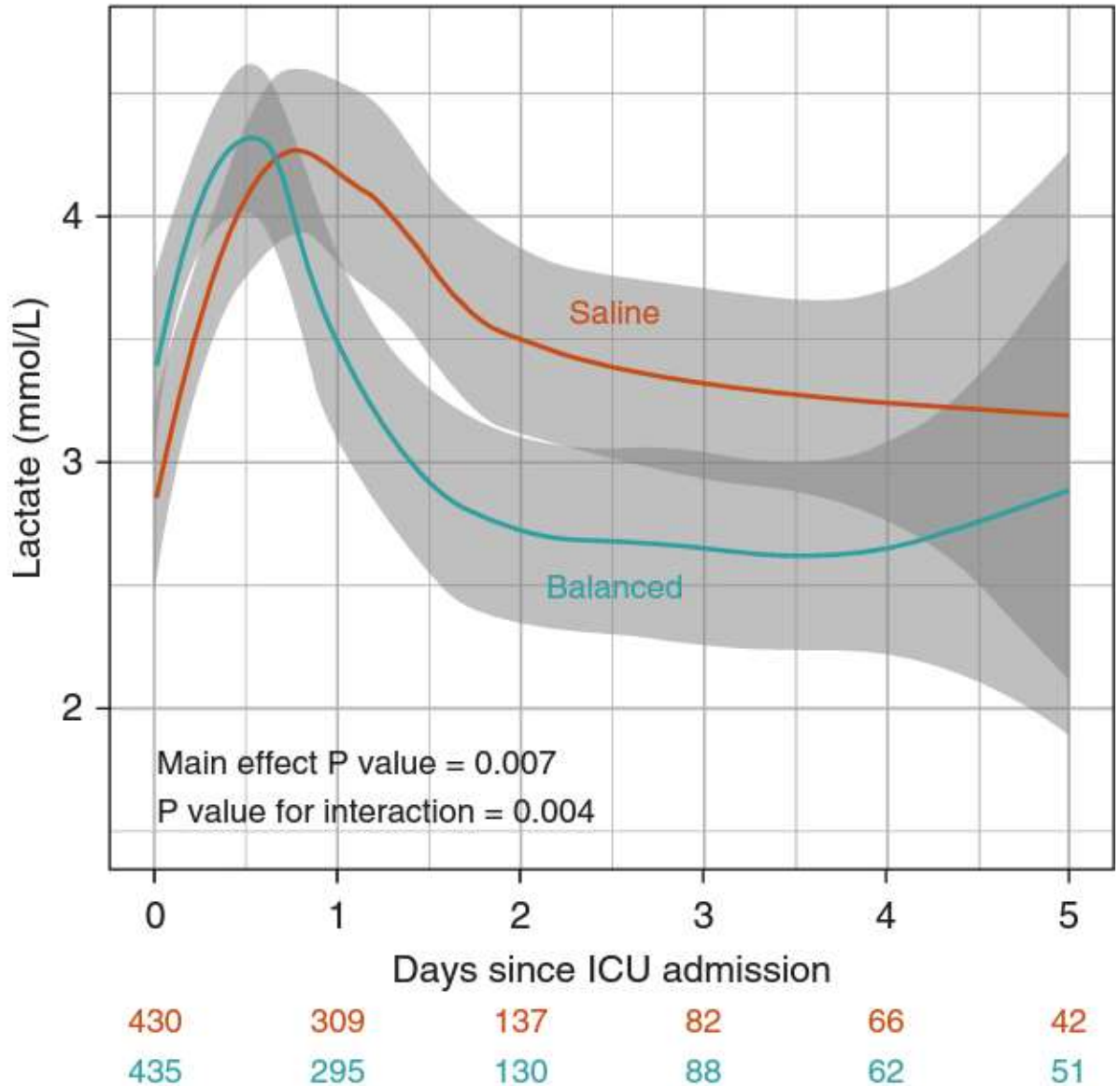

Brown *et al*. Am J Respir Crit Care Med 2019 Vol 200

LIMITATIONS

- A single centre, unblinded study
- The benefit of low chloride solution is via renoprotective mechanisms but in this study effect on 30-day in-hospital mortality was larger than effects on plasma creatinine and AKI
- Baseline serum chloride concentration has no effect on probability of in hospital mortality

LIMITATIONS

- Average patient received very small amount of fluid so its difficult to attribute mortality benefit solely to this
- With use of low chloride fluids, there is greater confidence in reduction of AKI (OR, 0.67; 95% CI, 0.49–0.92) but not regarding progression to receipt of renal replacement therapy (OR, 0.85; 95% CI, 0.71–1.03)

LIMITATIONS

- While focusing on patient centered outcome, keeping death equivalent to renal replacement therapy or doubling of creatinine level (subject to imputation bias) is matter of just metric
- Patient populations were categorized by hospital location which may not relate to severity of illness or to increased risk of adverse outcomes

THE RESULTS OF THIS STUDY SHOULD BE REGARDED AS HYPOTHESIS GENERATING

LIMITATIONS

- None of the currently available balanced crystalloid including compound sodium lactate (Ringer’s solution) and solutions in which anions such as acetate, gluconate, bicarbonate were substituted for lactate (Plasma-Lyte solutions) are truly buffered or balanced
- Hypotonic related to extracellular fluid and associated with generation of metabolic alkalosis

Myburgh et al. N ENGL J MED 378;9

Ongoing trials - PLUS

- Plasma-Lyte 148 versUs Saline Study (PLUS)
- Phase 4, randomized, parallel assignment, quadruple masking
- Recruitment from Sept 1, 2017 to March 2021
- Comparison of Plasmalyte 148 and Saline for fluid resuscitation and intravenous fluid therapy in critically ill adults
- Clinical Trial Number – NCT02721654

OUTCOMES-

- PRIMARY OUTCOME – Death from all causes (at 90 days after randomization)

- SECONDARY OUTCOMES–

1. Mean and peak creatinine concentration [first seven days]
2. ICU, hospital and 28 days all cause mortality [28 days and 6 months after randomization]
3. Duration of ICU stay [28 days and 90 days after randomization]

OUTCOMES-

4. Duration of hospital stay [28 days and 90 days after randomization]
5. Proportion of patients newly treated with renal replacement therapy
6. Duration of mechanical ventilation in ICU
7. Proportion of patients treated with and duration of vasoactive drugs

On going trials - BaSICS

- Randomised controlled, triple blinded trial
- **POPULATION**: Cohort of 11000 patients from 100 Brazilian ICUs
- **INTERVENTION**: Either Plasma-Lyte 148 or saline and to rapid infusion (999ml/hr) or slow infusion (333ml/hr)
- Study fluid will be used for resuscitation, dilution of compatible medications and maintainence solutions
- Clinical Trial number – NCT02875873

On going trials - BaSICs

• OUTCOME:

PRIMARY OUTCOME- 90 day all cause mortality

SECONDARY OUTCOME-

1. Incidence of renal failure requiring renal replacement therapy within 90 days
2. Incidence of acute kidney injury (KDIGO stages 2 and 3)
3. Incidence of non-renal organ dysfunction assessed by SOFA at day 3 and 7
4. Number of mechanical ventilation free days within 28 days of randomisation

ACETATE AS BUFFER

- After cellular uptake, two-carbon acetate anions forms acetyl CoA and enters citric acid cycle
- Final by-products, CO_2 and H_2O are in equilibrium with bicarbonate
- Infusion of sodium acetate increases strong ion difference by causing net increase in cations, as acetate anion is metabolized out of system
- Mode of metabolism not clear ? Hepatic ? Skeletal muscles

ACETATE AS BUFFER

- Adverse effects related to acetate were observed while its use as dialysate buffer
- Disreputed to cause myocardial depression, hypotension and hypopnea resulting in hypoxemia
- Sodium acetate in head to head comparison with sodium bicarbonate dialysate consistently lower SVR
- Flushing reactions observed by intravenous bolus; likely due to nitric oxide production
- Incidence of hyperpyrexia reported

Neavyn *et al. J* Med Toxicol 2013;9:250-4

COST ANALYSIS

- Most of the studies quoting balanced solutions used Ringer's lactate
- Cost of Ringer's lactate is same as that of normal saline
- Cost of Plasma-Lyte 148 is three times that of normal saline
- Considering the significant costs associated with critical care and associated poor clinical outcomes and adverse events, using normal saline or Ringer's lactate is cost effective intervention while considering balanced fluids

Myburgh et al. N ENGL J MED 378;9
Weinberg et.al. World J Crit Care Med. 2016 Nov 4; 5(4): 235-250

CONCLUSION

- Superiority of balanced fluids to saline cannot be established
- Lack of evidence supporting decrease in mortality, AKI or renal replacement therapy
- Need of well planned randomized trial taking in account cost of balanced fluids, amount of fluids administered and proposed benefit of renal protection with renal markers