A "Balanced" Approach to Fluids

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Objectives

Classify different crystalloid solutions used for resuscitation in critically ill patients

Examine the evidence evaluating the use of balanced crystalloid solutions in critically ill patients

Fluid Choices

	Plasma*	0.9% NaCl	Hartmann's	Lactated Ringer's (USP)	Ringer's acetate	Plasma-Lyte 148	Sterofundin ISO	0.18% NaCl/4% dextrose	Plasma-Lyte 56 Maintenance	0.45% saline	5% dextrose
Na^+ (mmol/l)	135-145	154	131	130	130	140	145	31	40	77	0
Cl^- (mmol/l)	95-105	154	111	109	112	98	127	31	40	77	0
$[Na^+]:[Cl^-]$ ratio	1.28-1.45:1	1:1	1.18:1	1.19:1	1.16:1	1.43:1	1.14:1	1:1	1:1	1:1	-
K^+ (mmol/l)	3.5-5.3	0	5	4	5	5	4	0	13	0	0
HCO_3^- / Bicarbonate precursor (mmol/l)	24-32	0	29 (lactate)	28 (lactate)	27 (acetate)	27 (acetate) 23 (gluconate)	24 (acetate) 5 (malate)	0	16 (acetate)	0	0
Ca^{2+} (mmol/l)	2.2-2.6	0	2	1.4	1	0	2.5	0	0	0	0
Mg^{2+} (mmol/l)	0.8-1.2	0	0	0	1	1.5	1	0	1.5	0	0
Glucose (mmol/l)	3.5-5.5	0	0	0	0	0	0	222.2 (40 g)	277.8 (50 g)	0	277.8 (50 g)
pH	7.35-7.45	4.5-7.0	5.0-7.0	6-7.5	6-8	4.0-8.0	5.1-5.9	4.5	3.5-6.0	4.5-7.0	3.5-5.5
Osmolarity (mOsm/l)	275-295	308	278	273	276	295	309	284	389	154	278

Chloride- The Neglected Electrolyte

Urinary dilution and concentration
- TALH
- 2 Cl^-:Na^+:K^+ co-transporter

Glomerular filtration
- Macula densa
- Tubuloglomerular feedback

pH balance
- Bicarbonate transport
- Gastric acid secretion

Nerve conduction velocity

Diagnostic evaluations
- Volume status
- Metabolic alkalosis
- Type of acid-base disorder (anion gap)

Metabolic acidosis
- Strong ion difference

Systemic hypotension

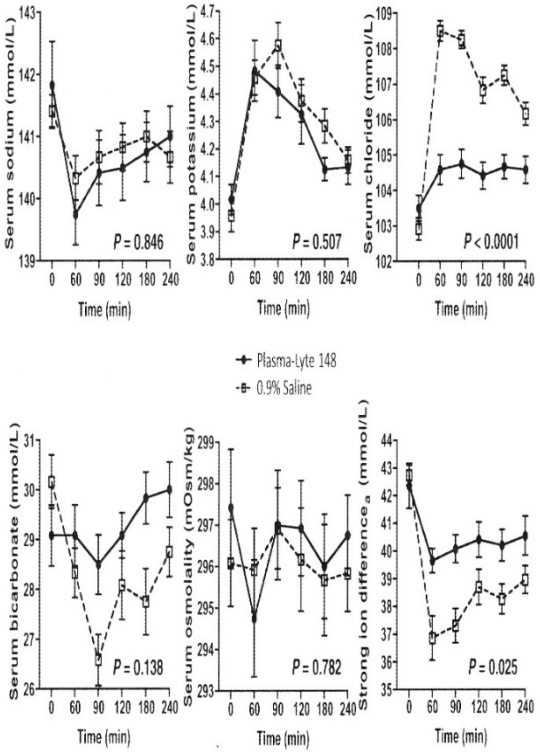
Inflammation
- Increased IL-6/IL-10 ratio
- NF-κB DNA binding

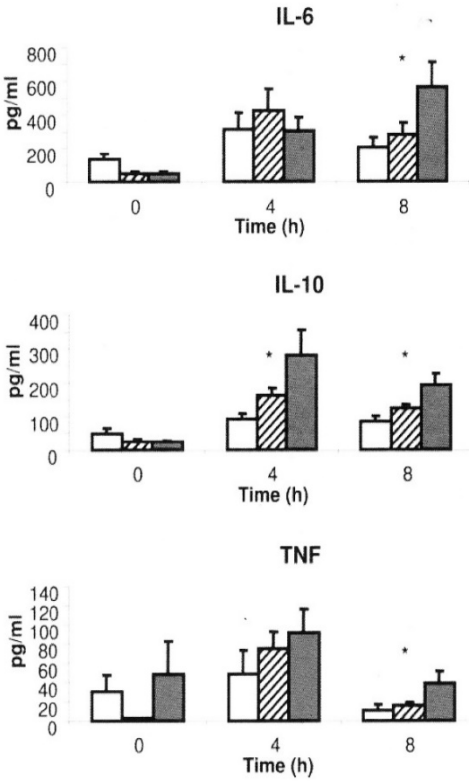
Renal effects
- Vasoconstriction
- Reduced GFR

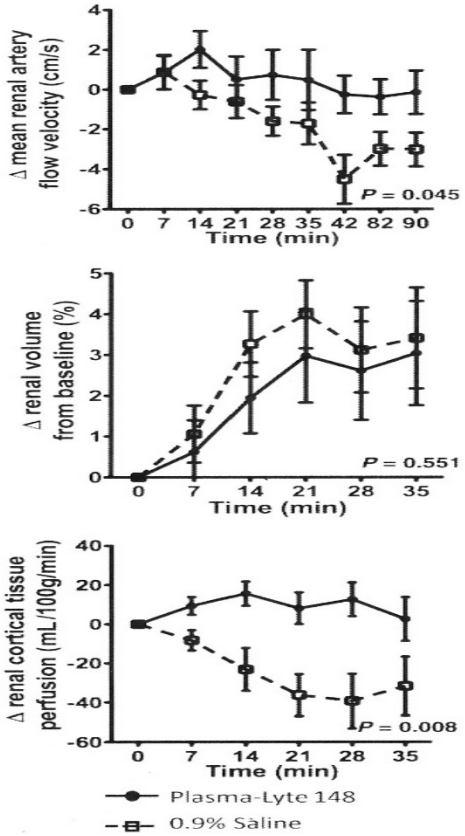
Reduced splanchnic perfusion

Reduced hemostasis

Effects of Chloride Infusion







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

Kellum J, et al. *Chest* 2006; 130: 962- 966

KDIGO Definition of AKI

Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) increase	$<$0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	$<$0.5 ml/kg/h for $\geqslant$12 hours
3	3.0 times baseline OR Increase in serum creatinine to $\geqslant$4.0 mg/dl ($\geqslant$353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients $<$18 years, decrease in eGFR to $<$35 ml/min per 1.73 m^2	$<$0.3 ml/kg/h for $\geqslant$24 hours OR Anuria for $\geqslant$12 hours

Kidney Intern Supplements; 2012: 2

Chloride Content and Surgery

Observational study

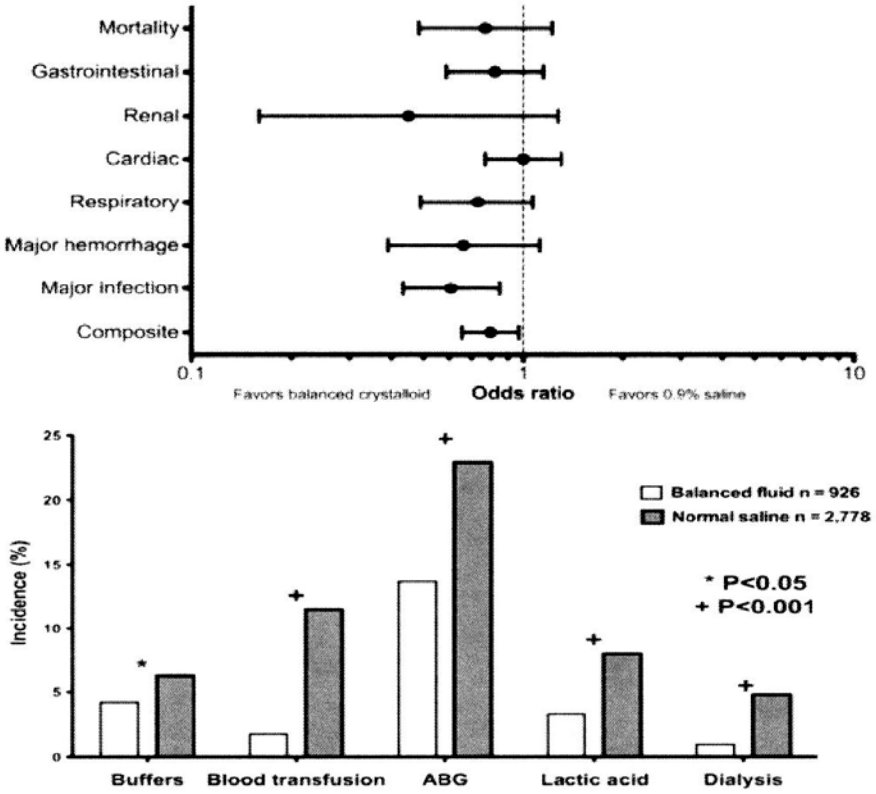
Premier Prospective Comparative Database

Major abdominal surgery

0.9% saline vs. balanced solution

467,131 cases
- 9,905- balanced solutions
- 346,901- 0.9% saline solution

Propensity matched 3:1
- 926- balanced solutions
- 2778- 0.9% saline solution



Shaw A, et al. *Ann Surg* 2012; 255: 821-829

Chloride Load and Mortality

Retrospective analysis

109,836 patients

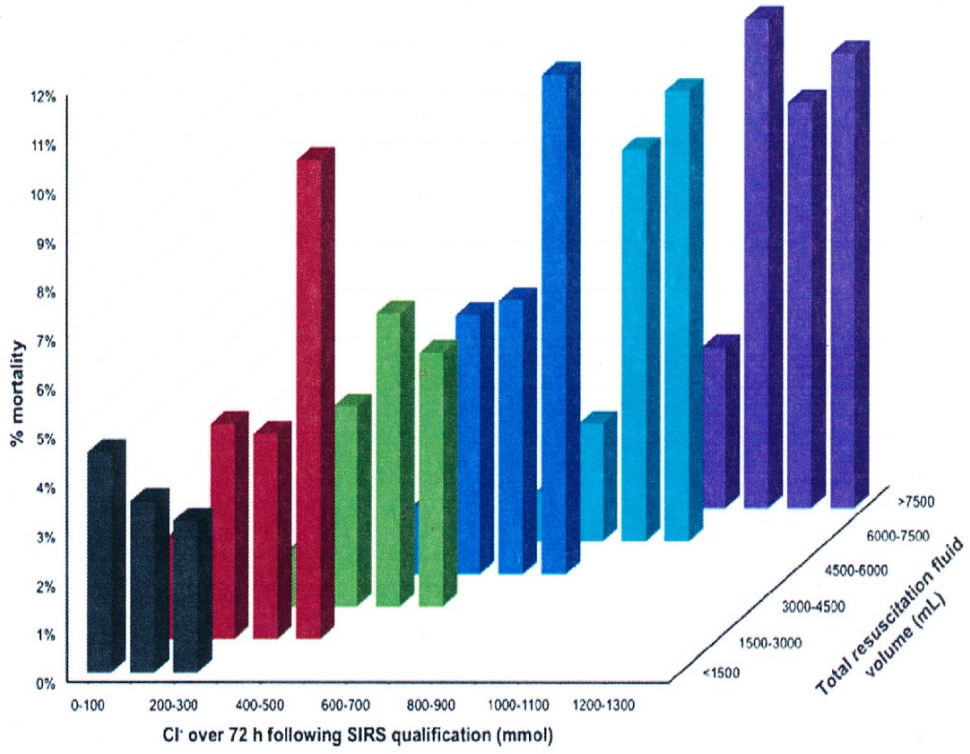
Met SIRS criteria

- Tachycardia plus:
  - Fever or hypothermia
  - Leukocytosis/leukopenia
  - Tachypnea/low PCO_2

Received > 500 ml

- Within 48 hours

APS adjusted mortality



Shaw, et al. *Intensive Care Med* 2014; 40: 1897-1905

Chloride Restriction and AKI

Prospective sequential pilot study

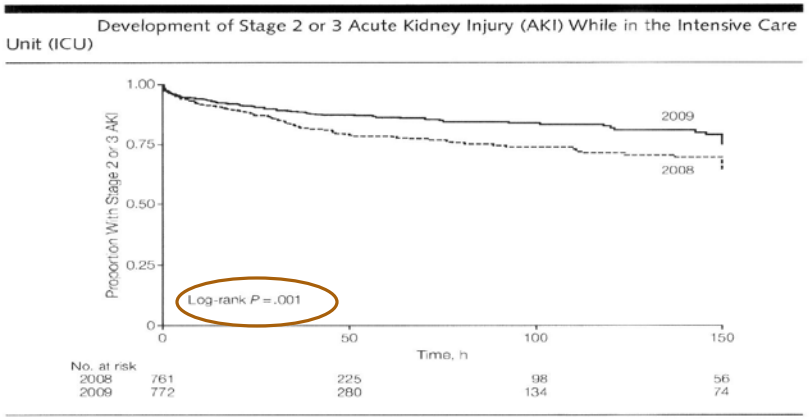
760 and 773 patients in each period

Chloride rich period:

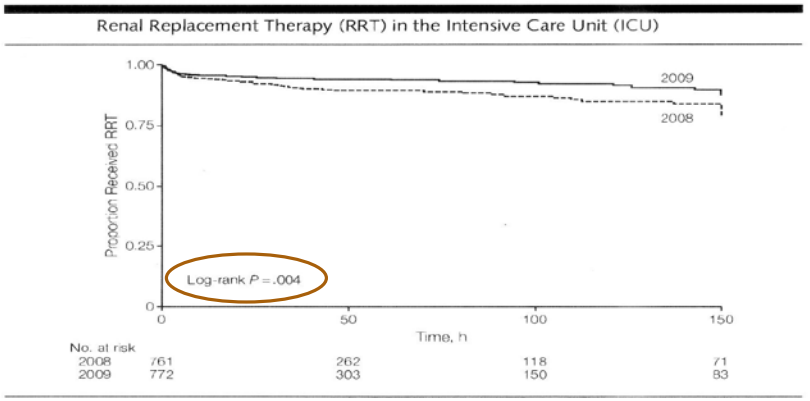
- 0.9% saline
- 4% gelatin
- 4% albumin

Chloride poor

- Lactated solution
- Plasma-lyte
- Chloride-poor 20% albumin



Stage 2 or 3 defined according to the Kidney Disease: Improving Global Outcomes clinical practice guideline.



Younos N, et al., *JAMA* 2012; 308: 1566-1572

Randomized Controlled Trials

What's the question they're asking?

- Physiological differences
- Acute kidney injury
- Mortality

Is it the right question to ask?

- Is it important from a patient perspective

Are they asking the question in the correct way?

- Study design
- Patient population

Will you believe the answer to the question at the end?

- Inclusion/exclusion criteria
- Power

Buffered Solution vs. Saline SPLIT Study

Randomized trial
- ANZIC Study group
- Masked
- Double cross over

2,091 ICU patients
- Mostly surgical
- Low co-morbidity
- Given “as needed”

Outcomes
- Stage 2 or 3 AKI
  - Overall 9% incidence
- RRT
  - Overall 3% incidence

Variable	No./Total No. (%) Buffered Crystalloid	Saline	Absolute Difference (95% CI)	Relative Risk (95% CI)	P Value
Primary Outcome					
Acute kidney injury or failure[a]	102/1067 (9.6)	94/1025 (9.2)	0.4 (−2.1 to 2.9)	1.04 (0.80 to 1.36)	.77
Secondary Outcomes (Renal Outcomes)					
RIFLE[b]					
Risk	123/1067 (11.5)	107/1025 (10.4)	1.1 (−1.6 to 3.8)	1.10 (0.86 to 1.41)	.44
Injury	46/1067 (4.3)	57/1025 (5.6)	−1.2 (−3.1 to 0.6)	0.78 (0.53 to 1.13)	.19
Failure	54/1067 (5.1)	36/1025 (3.5)	1.5 (−0.2 to 3.3)	1.44 (0.95 to 2.18)	.09
Loss	2/1067 (0.2)	1/1025 (0.1)	0	1.92 (0.17 to 21.16)	>.99
End-stage renal failure	0/1067 (0)	0/1025 (0)			
KDIGO stage[c]					
1	194/1067 (18.2)	194/1025 (18.9)	−0.7 (−4.1 to 2.6)	0.96 (0.80 to 1.15)	.69
2	43/1067 (4.0)	46/1025 (4.5)	−0.5 (−2.2 to 1.3)	0.90 (0.60 to 1.4)	.67
3	62/1067 (5.8)	58/1025 (5.7)	0.2 (−1.8 to 2.1)	1.03 (0.73 to 1.45)	.93
RRT use and indications for RRT initiation					
RRT use	38/1152 (3.3)	38/1110 (3.4)	−0.1 (−1.6 to 1.4)	0.96 (0.62 to 1.50)	.91
Oliguria	10/1152 (0.9)	11/1110 (1.0)	−0.1 (−0.9 to 0.7)	0.88 (0.37 to 2.03)	.83
Hyperkalemia with serum potassium >6.5 mEq/L	4/1152 (0.3)	2/1110 (0.2)	0.2 (−0.3 to 0.6)	1.93 (0.35 to 10.50)	.69
Acidemia with pH <7.20	13/1152 (1.1)	9/1110 (0.8)	0.3 (−0.5 to 1.1)	1.39 (0.60 to 3.24)	.52
Serum urea nitrogen >70 mg/dL	5/1152 (0.4)	10/1110 (0.9)	−0.5 (−1.1 to 0.2)	0.48 (0.17 to 1.41)	.20
Serum creatinine >3.39 mg/dL	16/1152 (1.4)	13/1110 (1.2)	0.2 (−0.7 to 1.1)	1.19 (0.57 to 2.45)	.71
Organ edema	6/1152 (0.5)	11/1110 (1.0)	−0.5 (−1.2 to 0.2)	0.53 (0.20 to 1.42)	.23
Other renal failure-related indication	3/1152 (0.3)	9/1110 (0.8)	−0.6 (−1.2 to 0.1)	0.32 (0.09 to 1.18)	.09
Other non-renal failure-related indication	0/1152 (0)	2/1110 (0.2)	−0.2 (−0.4 to 0.1)		.24
Ongoing use after hospital discharge	0/1152 (0)	0/1110 (0)			
Δ Creatinine, mean (95% CI), mg/dL[d]	0.21 (0.16 to 0.25)	0.18 (0.13 to 0.23)	0.03 (−0.04 to 0.10)[e]		.42
Service utilization, geometric mean (95% CI)					
ICU, d	1.50 (1.41 to 1.60)	1.47 (1.39 to 1.57)	1.02 (0.94 to 1.11)[f]		.58
Hospital, d	7.45 (7.05 to 7.87)	7.33 (6.94 to 7.76)	1.01 (0.94 to 1.10)[f]		.72
Mechanical ventilation, h	15.32 (13.83 to 16.97)	14.24 (12.82 to 15.82)	1.05 (0.91 to 1.21)[f]		.48
Use of mechanical ventilation	790/1152 (68.6)	751/1110 (67.7)	0.9 (−2.9 to 4.8)	1.01 (0.96 to 1.07)	.65
ICU readmission required during index hospital admission	80/1152 (6.9)	57/1110 (5.1)	1.8 (−0.2 to 3.8)	1.35 (0.97 to 1.88)	.08
Mortality					
Death in ICU	76/1152 (6.6)	80/1110 (7.2)	−0.6 (−2.7 to 1.5)	0.92 (0.68 to 1.24)	.62
Death in hospital	87/1152 (7.6)	95/1110 (8.6)	−1.0 (−3.3 to 1.2)	0.88 (0.67 to 1.17)	.40

Young, et al. *JAMA* 2015; 314: 1701-1710

How SPLIT Were They Really?

	Volume of fluid administered (mL) and proportion of patients receiving fluid– mean ± SD; median [IQR]; no. / total no. (%)	
Fluid	**Buffered crystalloid group**	**Saline group**
Plasma-Lyte 148 (study fluid)		
Day 0[a]	1711 ± 1385; 1250 [650-2500] 1152/1152 (100)	1 ± 45; 0 [0-0] 1/1110 (0)
Day 1	554 ± 1088; 40 [0-780] 562/1102 (51)	0 ± 15; 0 [0-0] 1/1056 (1)
Day 2	285 ± 606; 0 [0-320] 199/530 (38)	0 ± 0; 0 [0-0] 0/494 (0)
Day 3	157 ± 382; 0 [0-102] 89/323 (28)	0 ± 0; 0 [0-0] 0/300 (0)
Day 4 to 90	1285 ± 4590; 0 [0-850] 83/214 (39)	0 ± 0; 0 [0-0] 0/197 (0)
Total	2655 ± 3052; 2000 [1000-3500]	1.8 ± 60; 0 [0-0]
0.9% saline (study fluid)		
Day 0[a]	0 ± 0; 0 [0-0] 0/1152 (0)	1694 ± 1292; 1410 [750-2280] 1105/1110 (100)
Day 1	0 ± 1.5; 0 [0-0] 1/1152 (0)	564 ± 890; 95 [0-875] 572/1056 (54)
Day 2	0 ± 0; 0 [0-0] 0/530 (0)	295 ± 609; 0 [0-440] 176/494 (36)
Day 3	0 ± 0; 0 [0-0] 0/323 (0)	202 ± 542; 0 [0-85] 82/300 (27)
Day 4 to 90	2 ± 34; 0 [0-0] 1/214 (0)	777 ± 1615; 0 [0-760] 85/197 (43)
Total	0.5 ± 15; 0 [0-0]	2554 ± 2120; 2000 [1000-3250]

Young, et al. *JAMA* 2015; 314: 1701-1710

SALT Trial

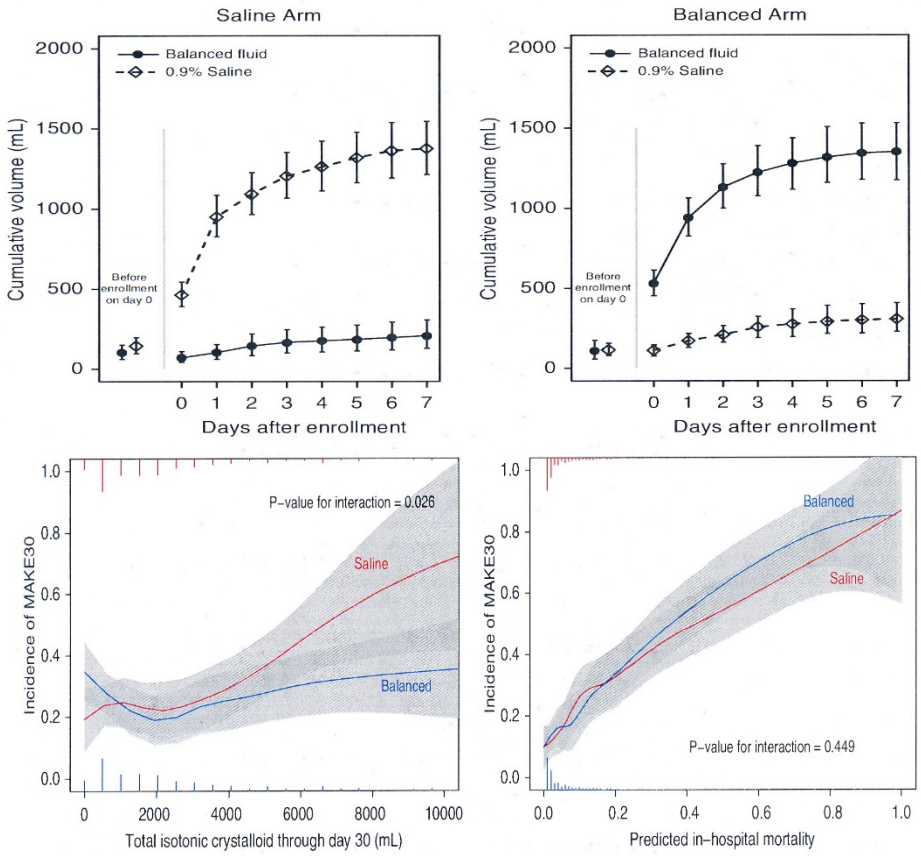
Cluster randomized cross over

974 adult ICU patients

Saline vs. LR or plasmalyte
- Alternated monthly
- Software tools within EHR

Primary outcome
- Proportion of crystalloid that was saline

Secondary outcome: MAKE30
- Death
- Dialysis
- Persistently reduced eGFR



Semler M, et al. *Am J Respir Crit Care Med* 2017; 195: 1362-1372

SALT-ED Trial- Not ICU

13,347 ED patients

Non-critically ill
- Transferred to non-ICU setting

Single center cross over design
- 16-month period

Balanced vs. crystalloids
- LR or Plasma-Lyte A vs. saline
- Alternate months

Primary endpoint
- Hospital-free days (alive after discharge before day 28)

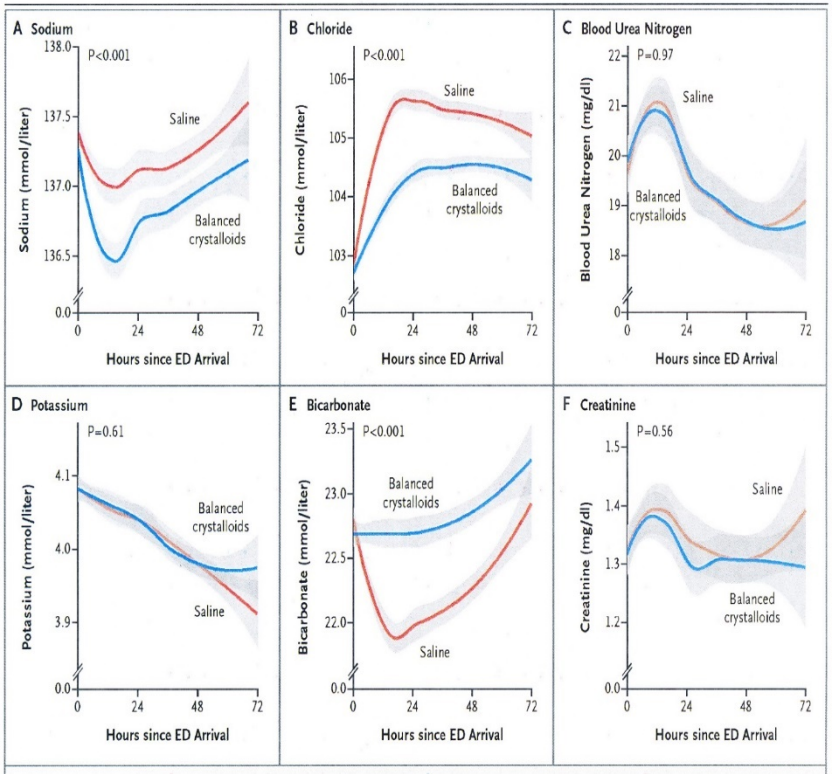
Secondary endpoint
- MAKE (at 30 days)
  - Death
  - RRT
  - Creatinine ≥ 200% of baseline

Crystalloids Received in the Emergency Department According to Assigned Treatment Group.*

Variable	Balanced Crystalloids (N=6708)	Saline (N=6639)
Total crystalloid volume		
Mean — ml	1608±1095	1597±1105
Median (IQR) — ml	1089 (1000–2000)	1071 (1000–2000)
≥2000 ml — no. (%)	2207 (32.9)	2150 (32.4)
Median volume of balanced crystalloids (IQR) — ml	1000 (1000–2000)	0
Median volume of saline (IQR) — ml	0	1000 (1000–2000)
Percentage of crystalloid volume consistent with assigned group — no. (%)		
100%: per-protocol population	5620 (83.8)	6160 (92.8)
51–99%	514 (7.7)	270 (4.1)
1–50%	254 (3.8)	131 (2.0)
0%	320 (4.8)	78 (1.2)

Self W, et al. *N Engl J Med* 2018; 378: 819-828

SALT-ED Results



Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

Outcome	Balanced Crystalloids (N=6708)	Saline (N=6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	94 (1.4)	102 (1.5)	0.89	
New renal-replacement therapy — no./total no. (%)†	18/6582 (0.3)	31/6530 (0.5)	0.56	
Final serum creatinine ≥200% of baseline — no./total no. (%)†	253/6582 (3.8)	293/6530 (4.5)	0.84	
Stage 2 or higher acute kidney injury — no./total no. (%)†	528/6582 (8.0)	560/6530 (8.6)	0.91 (0.80–1.03)	0.14
In-hospital death — no. (%)	95 (1.4)	105 (1.6)	0.88 (0.66–1.16)	0.36

Self W, et al. *N Engl J Med* 2018; 378: 819-828

SMART Trial- ICU

15,802 ICU patients (single center)
- 5 different ICUs

Pragmatic, cluster-randomized, multiple-crossover design

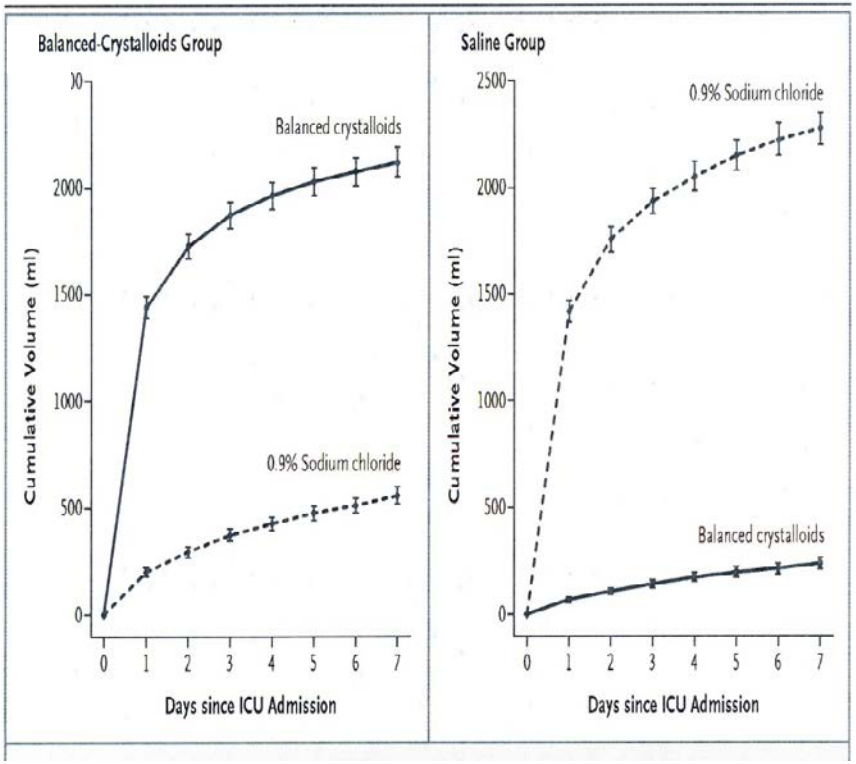
Balanced vs. 0.9% saline
- LR or Plasma-Lyte A
- Median volume 1,100 ml

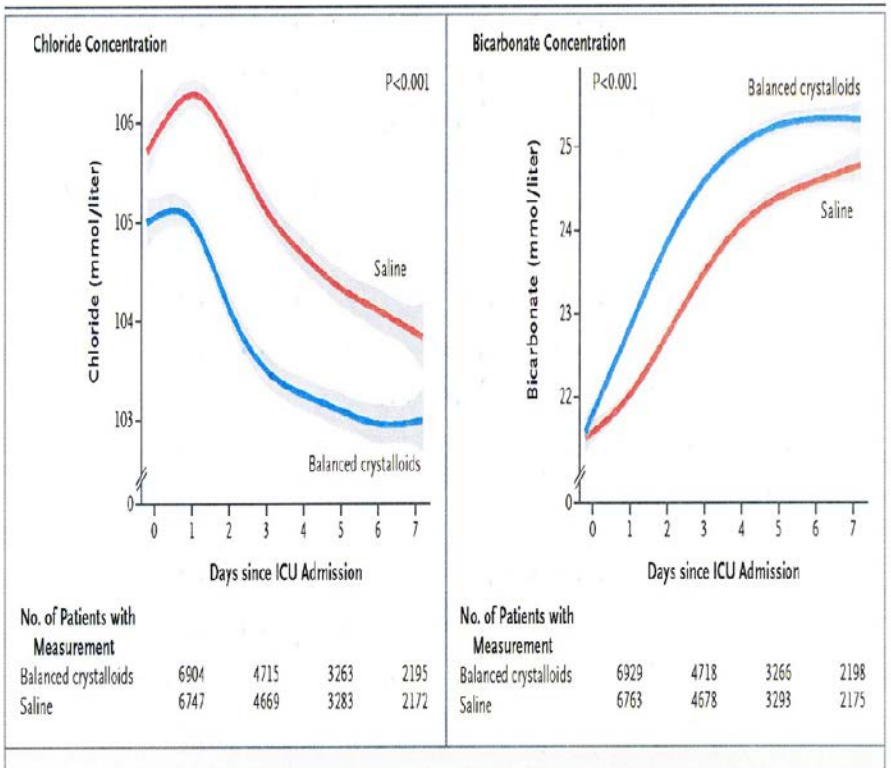
Primary outcome:
- MAKE at day 30
  - Death from any cause
  - RRT
  - Creatinine ≥ 200% of baseline

Outcome	Balanced N= 7942	Saline N= 7860	Odds ratio (95% CI)	P value
MAKE	14.3%	15.4%	0.90 (0.82-0.99)	0.04
30-day mortality	10.3%	11.1%	0.90 (0.80-1.01)	0.06
New RRT	2.5%	2.9%	0.84 (0.68-1.02)	0.08
Cr ≥ 200% of baseline	6.4%	6.6%	0.96 (0.84-1.11)	0.60

Semler M, et al. *N Engl J Med* 2018; 378: 829-839

SMART Details





No. of Patients with Measurement				
Balanced crystalloids	6904	4715	3263	2195
Saline	6747	4669	3283	2172

No. of Patients with Measurement				
Balanced crystalloids	6929	4718	3266	2198
Saline	6763	4678	3293	2175

Semler M, et al. *N Engl J Med* 2018; 378: 829-839

So…..

What's the question they're asking?

- Balanced is better than saline

Is it the right question to ask?

- Yes, if important issues are addressed

Are they asking the question in the correct way?

- I don't think so
- We need high risk, "high volume" patients

Do I believe the answer to the question at the end?

- Kind of because it fits my preconceived notions
- Most likely applies to populations not studied so far

How Much Fluid in the Wild?

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.72
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01

Rivers E, et al. *N Engl J Med* 2001; 345:1368

ProCESS Sepsis Trial

Intervention	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)	p-value[g]
Pre-randomization				
Intravenous fluids[b] — mL	2254 ± 1472	2226 ± 1363	2083 ± 1405	0.15
Fluids per body weight (mL/kg)	30.5 ± 22.3	29.2 ± 19.1	28 ± 21	
Vasopressor use[c]	84 (19.1)	75 (16.8)	69 (15.1)	0.28
Dobutamine use	0 (0)	0 (0)	0 (0)	
Blood transfusion	5 (1.1)	7 (1.6)	9 (2.0)	0.63
Mechanical ventilation	60 (13.7)	65 (14.6)	63 (13.8)	0.93
Intravenous antibiotics	332 (75.6)	343 (76.9)	347 (76.1)	0.91
Corticosteroids	41 (9.3)	42 (9.4)	38 (8.3)	0.82
Activated protein C	0 (0)	0 (0)	0 (0)	
Randomization to hour 6[d]				
Resuscitation elements				
Central venous catheterization	411 (93.6)	252 (56.5)	264 (57.9)	<0.0001
Central venous oximeter catheterization[e]	409 (93.2)	18 (4.0)	16 (3.5)	<0.0001
Intravenous fluids — mL	2805 ± 1957	3285 ± 1743	2279 ± 1881	<0.0001
Vasopressor use	241 (54.9)	233 (52.2)	201 (44.1)	0.003
Dobutamine use	35 (8)	5 (1.1)	4 (0.9)	<0.0001
Blood transfusion	63 (14.4)	37 (8.3)	34 (7.5)	0.001
Ancillary care				
Mechanical ventilation	116 (26.4)	110 (24.7)	99 (21.7)	0.25
Tidal volume, mL/kg predicted body weight[f]	8.5 ± 2.4	8.1 ± 1.6	8.0 ± 1.8	0.11
Tidal volume, mL/kg body weight	6.7 ± 2.1	6.5 ± 1.9	6.8 ± 2.1	0.32
Intravenous antibiotics	428 (97.5)	433 (97.1)	442 (96.9)	0.90
Corticosteroids	54 (12.3)	48 (10.8)	37 (8.1)	0.16
Activated protein C	1 (0.2)	1 (0.2)	0 (0)	0.55
Processes of care from 6-72 h				
Intravenous fluids — mL	4458 ± 3878	4918 ± 4308	4354 ± 3882	0.08
Vasopressor use	209 (47.6)	208 (46.6)	197 (43.2)	0.38
Dobutamine use	19 (4.3)	9 (2.0)	10 (2.2)	0.08
Blood transfusion	87 (19.8)	93 (20.9)	82 (18.0)	0.54
Mechanical ventilation	148 (33.7)	140 (31.4)	127 (27.9)	0.16
Tidal volume, mL/kg predicted body weight	8.5 ± 2.5	8.6 ± 2.6	8.1 ± 1.8	0.05
Tidal volume, mL/kg body weight	6.7 ± 2.3	6.6 ± 2.4	6.6 ± 2.2	0.81
Processes of care from 0-72 h				
Intravenous fluids — mL	7253 ± 4605	8193 ± 4989	6633 ± 4560	<0.0001
Vasopressor use	265 (60.4)	273 (61.2)	245 (53.7)	0.05
Dobutamine use	41 (9.3)	11 (2.5)	13 (2.9)	<0.0001
Blood transfusion	120 (27.3)	107 (24.0)	102 (22.4)	0.22
Mechanical ventilation	159 (36.2)	152 (34.1)	135 (29.6)	0.10
Tidal volume, mL/kg predicted body weight	8.5 ± 2.5	8.4 ± 2.4	8.1 ± 1.8	0.03
Tidal volume, mL/kg body weight	6.7 ± 2.2	6.6 ± 2.2	6.7 ± 2.2	0.55

Yealy D, et al. *N Engl J Med* 2014; 370: 1683-1693

ARISE Sepsis Trial

Characteristics of the Patients at Baseline.*

Characteristic	EGDT (N = 793)	Usual Care (N = 798)
Age — yr	62.7±16.4	63.1±16.5
Male sex — no. (%)	477 (60.2)	473 (59.3)
Usual residence — no. (%)		
Home	749 (94.5)	759 (95.1)
Long-term care facility	44 (5.5)	39 (4.9)
Median score on Charlson comorbidity index (IQR)†	1 (0–2)	1 (0–2)
APACHE II score‡	15.4±6.5	15.8±6.5
Mechanical ventilation — no. (%)		
Invasive	71 (9.0)	64 (8.0)
Noninvasive	60 (7.6)	48 (6.0)
Vasopressor infusion — no. (%)§	173 (21.8)	173 (21.7)
Total intravenous fluids¶		
Volume — ml	2515±1244	2591±1331
Volume per weight — ml/kg	34.6±19.4	34.7±20.1
Inclusion criteria‖		
Refractory hypotension — no. (%)	555 (70.0)	557 (69.8)
Systolic blood pressure — mm Hg	78.8±9.3	79.6±8.4
Lactate		
≥4.0 mmol/liter — no. (%)	365 (46.0)	371 (46.5)
Value at time that criterion was met — mmol/liter	6.7±3.3	6.6±2.8
Median interval after presentation to emergency department (IQR) — hr		
Until final inclusion criterion was met	1.4 (0.6–2.5)	1.3 (0.5–2.4)
Until randomization	2.8 (2.1–3.9)	2.7 (2.0–3.9)

Intervention	0 to 6 hours			6 to 72 hours[b]		
	EGDT (N = 793)	Usual care (N = 798)	P Value	EGDT (N = 782)	Usual care (N = 778)	P Value
Supplemental oxygen - no./total no. (%)	629/687 (91.6)	554/609 (91.0)	0.71	533/610 (87.4)	494/569 (86.8)	0.78
Mechanical ventilation - no./total no.						
Invasive	176/793 (22.2)	179/798 (22.4)	0.91	211/782 (27.0)	210/778 (27.0)	1.00
Non-invasive	100/793 (12.6)	84/798 (10.5)	0.19	91/782 (11.6)	106/778 (13.6)	0.24
Intravenous fluids,[c]						
Total - ml	1964 ±1415	1713 ± 1401	<0.001	4274 ± 3071	4382 ± 3136	0.51
Total - ml/kg	26.8 ± 20.6	23.2 ± 21.2	<0.001	58.9 ± 46.2	59.2 ± 45.1	0.87
Crystalloids - ml	1547 ± 1351	1374 ± 1335	0.01	3520 ± 2792	3608 ± 2783	0.54
Crystalloids - ml/kg	21.1 ± 19.8	18.7 ± 19.9	0.02	48.7 ± 42.3	48.8 ± 39.1	0.93
Colloids - ml	323 ± 672	249 ± 552	0.02	345 ± 777	328 ± 808	0.68
Colloids - ml/kg	4.4 ± 8.9	3.3 ± 7.5	0.01	4.8 ± 10.6	4.5 ± 11.2	0.63
Vasopressor infusion - no./total no. (%)[d]	528/793 (66.6)	461/798 (57.8)	<0.001	460/782 (58.8)	401/778 (51.5)	0.004
Blood products						
Red-cell transfusion - no./total no. (%)	108/793 (13.6)	56/798 (7.0)	<0.001	86/782 (11.0)	92/778 (11.8)	0.61
Red-cell transfusion volume - ml	56.1 ± 164	40.2 ± 167	0.06	57.6 ± 211.5	76.9 ± 280.0	0.12
Platelet transfusion - no./total no. (%)	34/793 (4.3)	28/798 (3.5)	0.42	47/782 (6.0)	48/778 (6.2)	0.90
Fresh frozen plasma - no./total no. (%)	41/793 (5.2)	35/798 (4.4)	0.46	43/782 (5.5)	50/778 (6.4)	0.44
Dobutamine infusion - no./total no. (%)	122/793 (15.4)	21/798 (2.6)	< 0.001	74/782 (9.5)	39/788 (5.0)	<0.001
Monitoring inserted - no./total no[e]						
Arterial catheter	725/793 (91.4)	609/798 (76.3)	< 0.001	9/782 (1.2)	32/778 (4.10)	<0.001
Central venous catheter	109/793 (13.7)	494/798 (61.9)	< 0.001	11/782 (1.4)	36/778 (4.6)	< 0.001
$ScvO_2$ central venous catheter[f]	714/793 (90.0)	3/798 (0.4)	< 0.001	0/782 (0)	0/778 (0)	1.00
Pulmonary artery catheter	1/793 (0.1)	9/798 (1.1)	0.01	3/782 (0.4)	7/778 (0.9)	0.20
PiCCO	20/793 (2.5)	22/798 (2.8)	0.77	24/782 (3.1)	27/778 (3.5)	0.66

ANZICS Group *N Engl J Med* 2014; 371: 1496- 1506

ProMISe Sepsis Trial

	Baseline		Hour 0 to hour 6		Hour 6 to hour 72		Hour 0 to hour 72	
	EGDT (N = 625)	Usual resuscitation (N= 626)	EGDT (N = 625)	Usual resuscitation (N= 626)	EGDT (N = 608)	Usual resuscitation (N= 607)	EGDT (N = 625)	Usual resuscitation (N= 626)
Total intravenous fluid† - no./total no. (%)	612/625 (97.9)	606/625 (97.0)	609/623 (97.8)	604/625 (96.6)	546/603 (90.5)	548/603 (90.9)	615/623 (98.7)	618/625 (98.9)
Total intravenous fluid - mL	1890±1105	1965±1149	2226±1443	2022±1271	4215±3068	4366±3114	5946±3740	5844±3651
Median total intravenous fluid (IQR) - mL	1950 (1000, 2500)	2000 (1000, 2500)	2000 (1150, 3000)	1784 (1075, 2775)	3623 (1800, 6060)	3981 (1895, 6291)	5587 (2915, 8150)	5410 (3000, 7970)
Intravenous colloid‡ - no./total no. (%)	---	---	197/623 (31.6)	180/625 (28.8)	171/603 (28.4)	150/603 (24.9)	260/623 (41.7)	240/625 (38.4)
Intravenous colloid - mL	---	---	1062±801	913±627	1207±1042	1093±1012	1598±1391	1369±1150
Median intravenous colloid (IQR) - mL	---	---	1000 (500, 1500)	750 (500, 1000)	750 (500, 1750)	750 (500, 1500)	1000 (575, 2000)	1000 (500, 1750)
Intravenous crystalloid‡ - no./total no. (%)	---	---	584/623 (93.7)	597/625 (95.5)	537/603 (89.1)	543/603 (90.0)	609/623 (97.8)	617/625 (98.7)
Intravenous crystalloid - mL	---	---	1963±1357	1767±1178	3909±2869	4136±2914	5323±3518	5317±3435
Median intravenous crystalloid (IQR) - mL	---	---	1750 (999, 2750)	1500 (900, 2380)	3403 (1576, 5647)	3694 (1832, 5911)	4864 (2520, 7241)	4900 (2700, 7408)
Vasopressors - no./total no. (%)	15/625 (2.4)	21/626 (3.4)	332/623 (53.3)	291/625 (46.6)	349/603 (57.9)	317/603 (52.6)	377/623 (60.5)	344/625 (55.0)
Red cell transfusion - no./total no. (%)	---	---	55/623 (8.8)	24/625 (3.8)	76/603 (12.6)	51/603 (8.5)	107/623 (17.2)	65/625 (10.4)
Red cells transfusion- mL	---	---	426±209	540±294	487±335	606±403	565±393	674±506
Median red cell transfusion (IQR) - mL	---	---	309 (285, 577)	535 (305, 607)	351 (291, 579)	552 (317, 620)	529 (298, 602)	562 (317, 660)
Dobutamine - no./total no. (%)	2/625 (0.3)	0/626 (0.0)	113/623 (18.1)	24/625 (3.8)	107/603 (17.7)	39/603 (6.5)	139/623 (22.3)	44/625 (7.0)

Mouncey P, et al. *N Engl J Med* 2015; 372: 1301-11

Adding It All Up

Study	Mortality	Pre-randomized fluids (ml)	0-6 hour fluid (ml)	7-72 hour fluid (mL)	Total Fluids (ml)	AKI (RRT)
Rivers	46% (60-day)	?	4,250	9,600	13,850	NR
ProCESS	19% (60-day)	2,100	2,800	4,500	9,400	4%
ARISE	19% (90-day)	2,500	1,800	4,300	8,600	13.5%
ProMISe	29% (90-day)	2,000	1,900	3,800	7,700	13.7%

Apples and Elephants

Study	Total volume (ml)	RRT	AKI (KDIGO stage ≥ 2	Mortality
SPLIT	2,500	3%	9%	8%
SALT	1,520	3.9%	19%	17.5%
SALT-ED	1,100	0.4%	8%	1.5%
SMART	1,100	2.5%	6.5%	10%
Rivers	13,850	NR	NR	46%
ProCESS	9,400	4%	NR	19%
ARISE	8,600	13.5%	NR	19%
ProMISe	7,700	13.7%	NR	29%

Barone J. *Br Med J* 2000; 321: 1569

Summary

High chloride solutions are not physiologic (not normal)

There are established negative effects of chloride administration

- Animal studies
- Limited human studies

Administration of high chloride containing solutions is associated with significant adverse events in large observation trials compared to balanced solutions

The negative effects of high chloride containing solutions on clinical outcomes in randomized controlled trials are less obvious.

Randomized controlled trials may not have enrolled the appropriate patients. Overall fluid volumes were low

Really sick patients at risk for AKI (and other complications) who will receive large amounts of volume, should receive balanced solutions.

Learning Assessment Questions

Which of the following is NOT associated with the administration of high chloride containing intravenous solutions?

A. Reduced renal blood flow

B. Development of a metabolic alkalosis

C. Increased production of IL-6 (interleukin 6)

D. Development of AKI (acute kidney injury)

Critically ill patients are less likely to develop AKI (acute kidney injury) when fluid resuscitated with 0.9% saline (normal saline).

A. True

B. False