

SUMMARY OF LANDMARK STUDIES ON FLUID THERAPY



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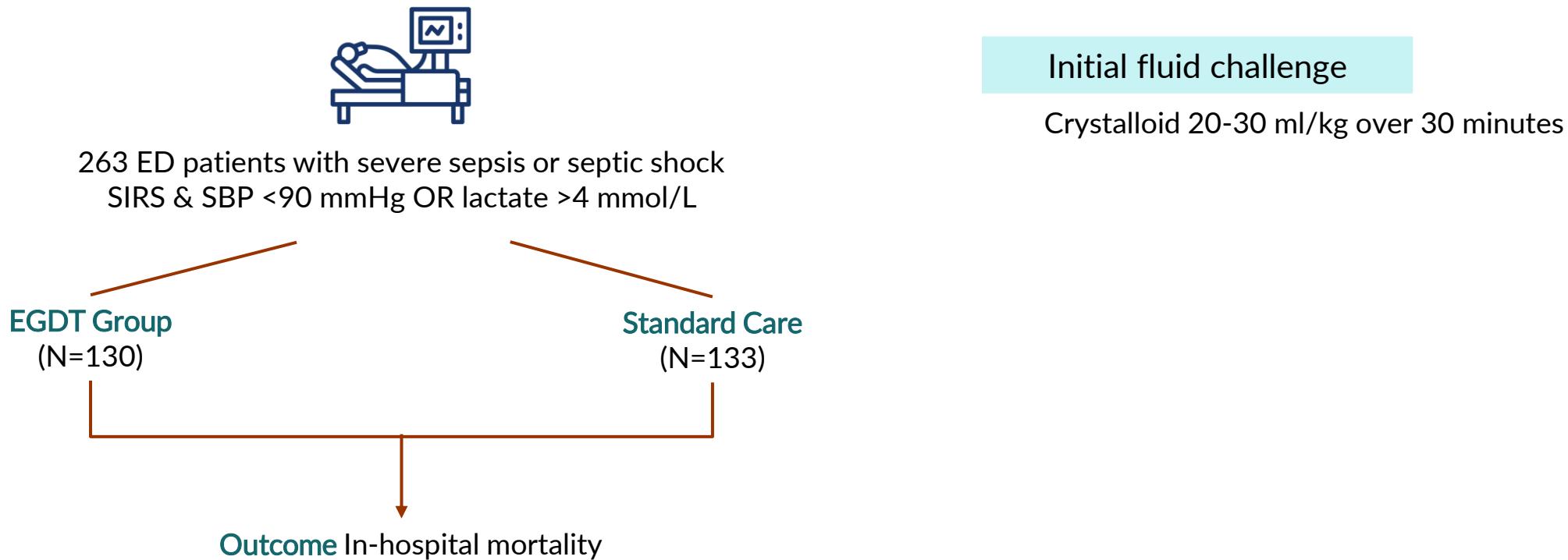
Early Goal-Directed Therapy (EGDT)

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Rivers Study

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Rivers et al
NEJM, Nov 8, 2001

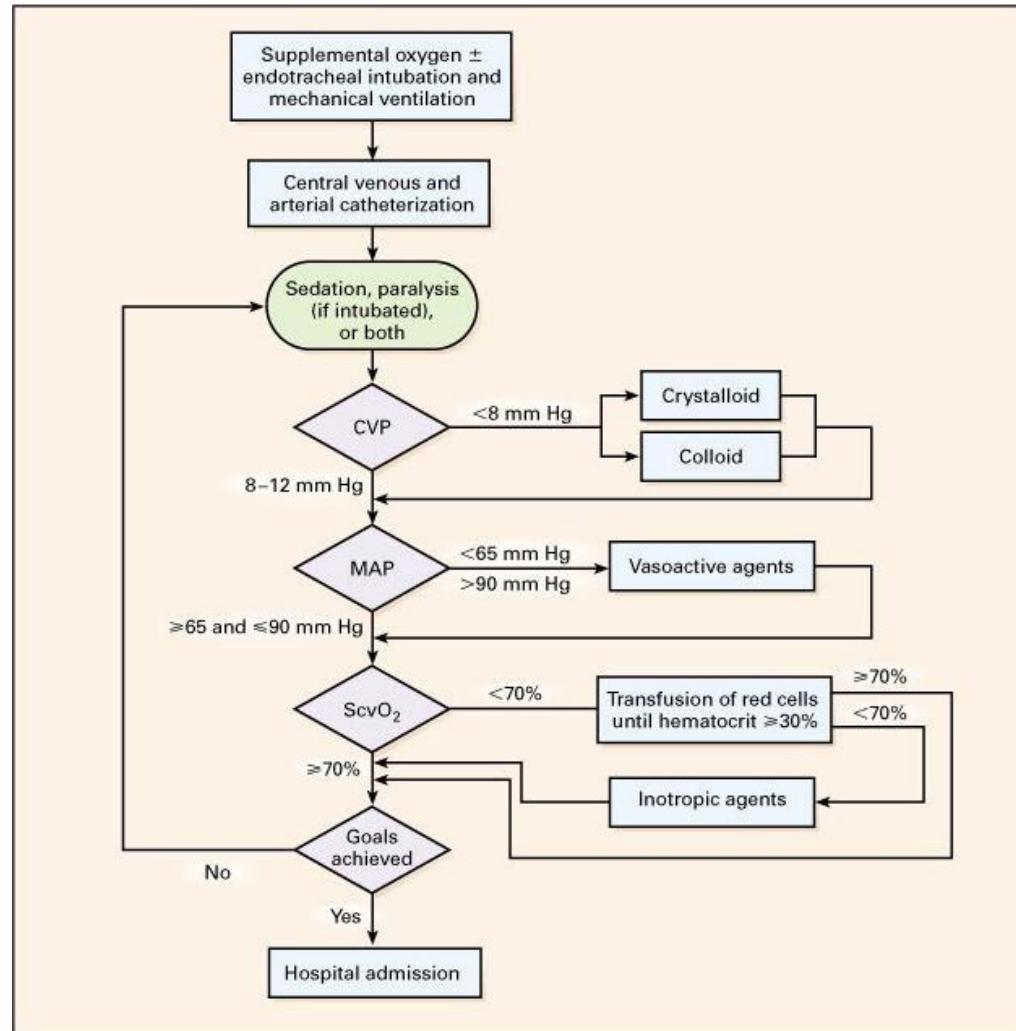


EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Rivers et al
NEJM, Nov 8, 2001



Protocol for Early Goal-Directed Therapy



EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Rivers et al

NEJM, Nov 8, 2001



TABLE 3. KAPLAN-MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan-Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

OUTCOMES

- Mean fluid in 6 h = 5 L
- In-hospital mortality was significant lower in EGDT group : 30.5% vs 46.5% (p=0.009)
- Same as 28-d mortality (p=0.1) and 60-d mortality (p=0.03)
- Significantly higher rate of organ failure during 7-72 h in standard therapy group (p<0.001)

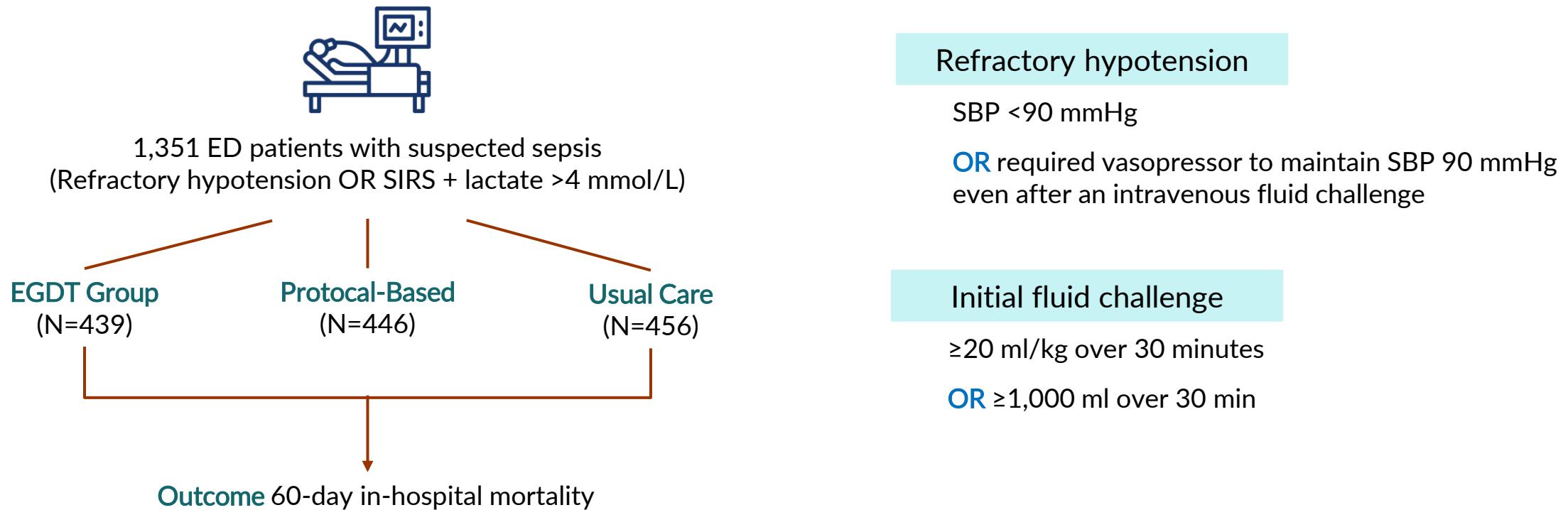
Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock

2 ProCESS Trial

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

ProCESS Study
NEJM, May 1, 2014



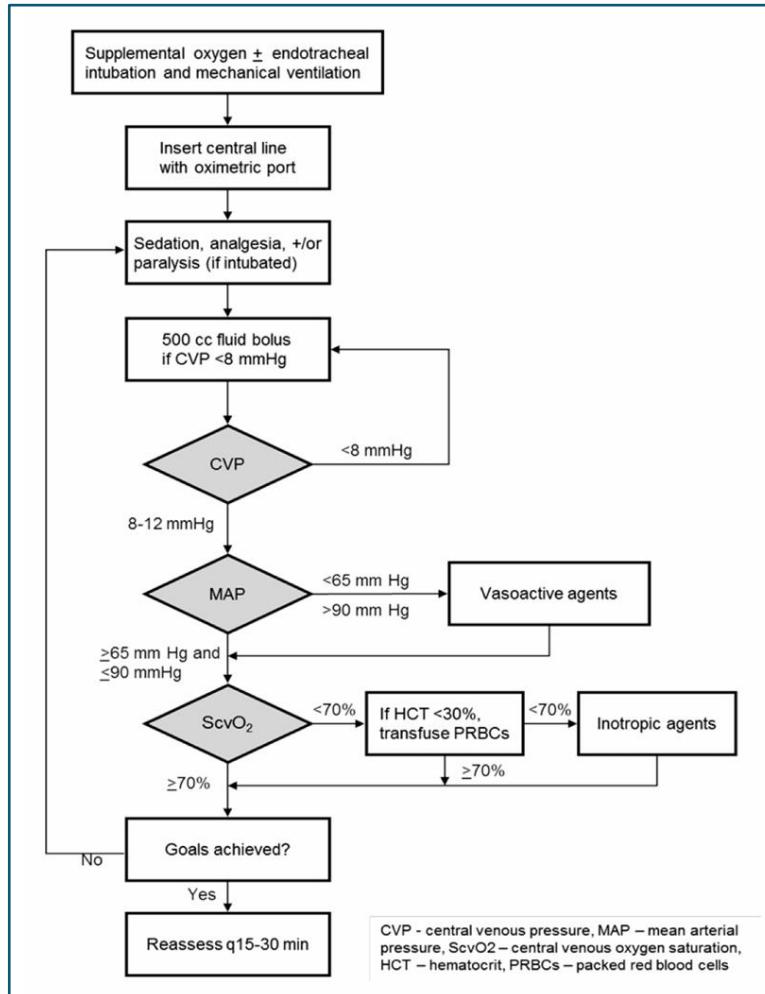
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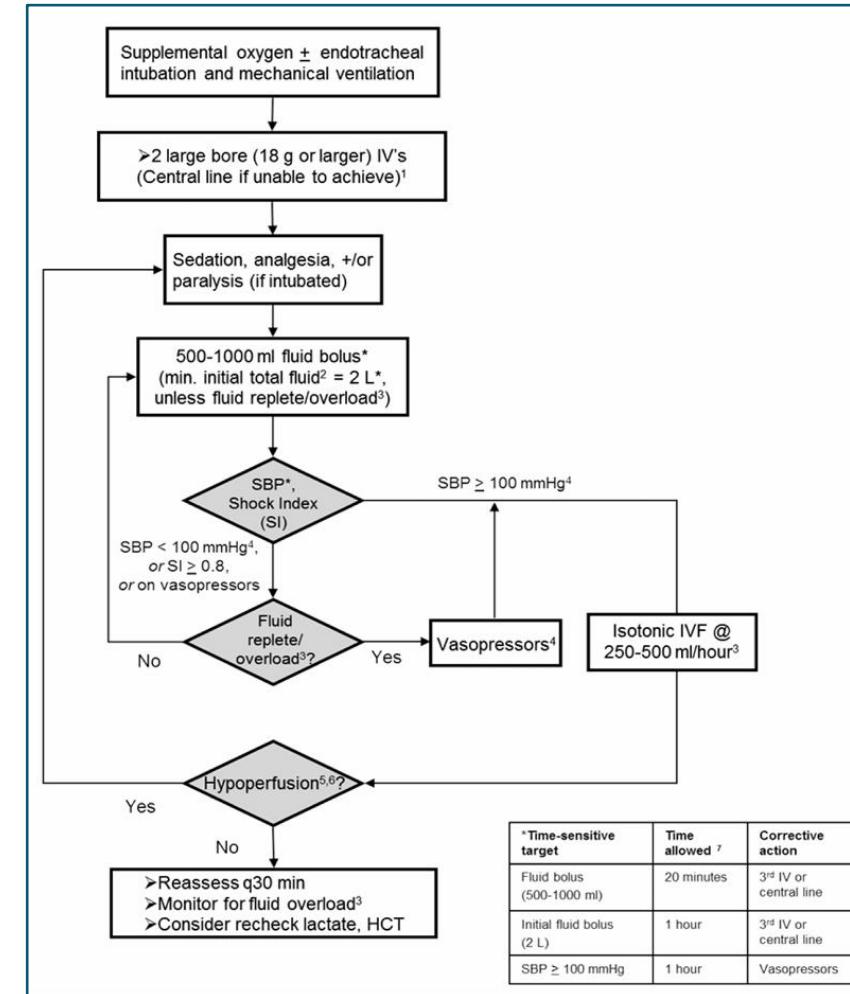
ProCESS Study
NEJM, May 1, 2014



EGDT



Protocol-based



A Randomized Trial of Protocol-Based Care for Early Septic Shock

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ProCESS Study
NEJM, May 1, 2014



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Protocol-Based EGDT (N=439)	Protocol-Based Standard Therapy (N=446)	Usual Care (N=456)
Age — yr†	60±16.4	61±16.1	62±16.0
Male sex — no. (%)	232 (52.8)	252 (56.5)	264 (57.9)
Residence before admission — no. (%)‡			
Nursing home	64 (14.6)	72 (16.1)	73 (16.0)
Other	373 (85.0)	373 (83.6)	382 (83.8)
Charlson comorbidity score§	2.6±2.6	2.5±2.6	2.9±2.6
Source of sepsis — no. (%)			
Pneumonia	140 (31.9)	152 (34.1)	151 (33.1)
Urinary tract infection	100 (22.8)	90 (20.2)	94 (20.6)
Intraabdominal infection	69 (15.7)	57 (12.8)	51 (11.2)
Infection of unknown source	57 (13.0)	47 (10.5)	66 (14.5)
Skin or soft-tissue infection	25 (5.7)	33 (7.4)	38 (8.3)
Catheter-related infection	11 (2.5)	16 (3.6)	11 (2.4)
Central nervous system infection	3 (0.7)	3 (0.7)	4 (0.9)
Endocarditis	1 (0.2)	3 (0.7)	3 (0.7)
Other	28 (6.4)	31 (7.0)	26 (5.7)
Determined after review not to have infection	5 (1.1)	14 (3.1)	12 (2.6)
Positive blood culture — no. (%)	139 (31.7)	126 (28.3)	131 (28.7)
APACHE II score¶	20.8±8.1	20.6±7.4	20.7±7.5
Entry criterion — no. (%)			
Refractory hypotension	244 (55.6)	240 (53.8)	243 (53.3)
Hyperlactatemia	259 (59.0)	264 (59.2)	277 (60.7)
Physiological variables			
Systolic blood pressure — mm Hg	100.2±28.1	102.1±28.7	99.9±29.5
Serum lactate — mmol/liter**	4.8±3.1	5±3.6	4.9±3.1
Time to randomization — min			
From arrival in the emergency department	197±116	185±112	181±97
From meeting entry criteria	72±77	66±38	69±45

A Randomized Trial of Protocol-Based Care for Early Septic Shock

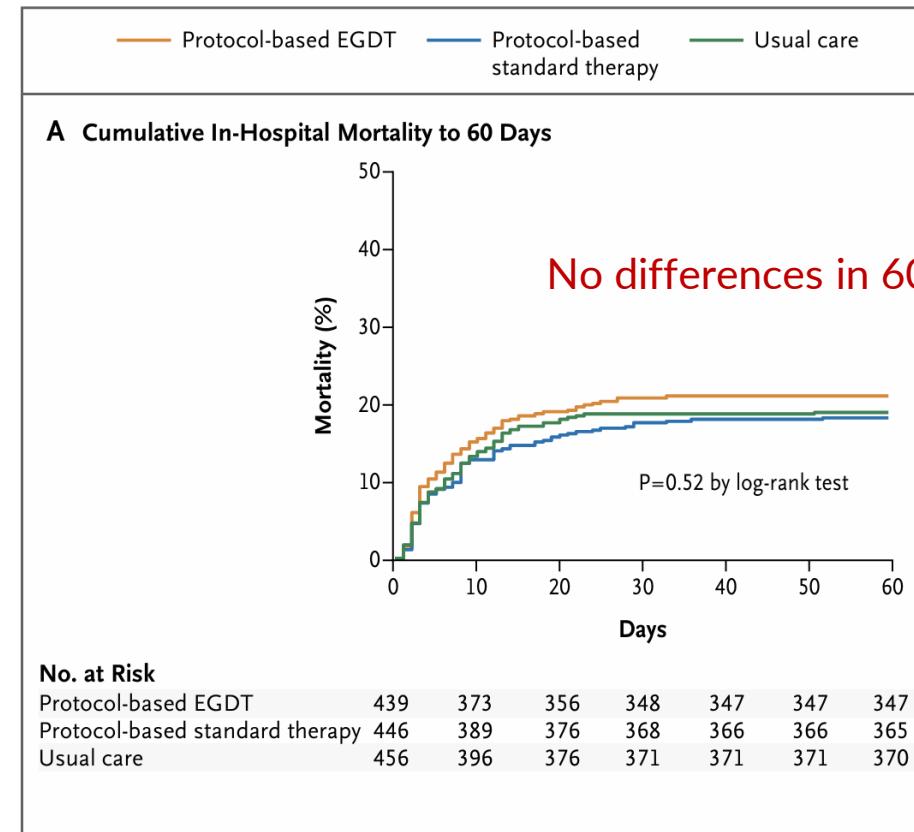
ProCESS Study
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Table 2. Outcomes.*

Outcome	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual Care (N=456)	P Value†
Death — no./total no. (%)				
In-hospital death by 60 days: primary outcome	92/439 (21.0)	81/446 (18.2)	86/456 (18.9)	0.83‡
Death by 90 days	129/405 (31.9)	128/415 (30.8)	139/412 (33.7)	0.66
New organ failure in the first week — no./total no. (%)				
Cardiovascular	269/439 (61.3)	284/446 (63.7)	256/456 (56.1)	0.06
Respiratory	165/434 (38.0)	161/441 (36.5)	146/451 (32.4)	0.19
Renal	12/382 (3.1)	24/399 (6.0)	11/397 (2.8)	0.04
Duration of organ support — days§				
Cardiovascular	2.6±1.6	2.4±1.5	2.5±1.6	0.52
Respiratory	6.4±8.4	7.7±10.4	6.9±8.2	0.41
Renal	7.1±10.8	8.5±12	8.8±13.7	0.92
Use of hospital resources				
Admission to intensive care unit — no. (%)	401 (91.3)	381 (85.4)	393 (86.2)	0.01
Stay in intensive care unit among admitted patients — days	5.1±6.3	5.1±7.1	4.7±5.8	0.63
Stay in hospital — days	11.1±10	12.3±12.1	11.3±10.9	0.25
Discharge status at 60 days — no. (%)				
Not discharged	3 (0.7)	8 (1.8)	2 (0.4)	0.82
Discharged to a long-term acute care facility	16 (3.6)	22 (4.9)	22 (4.8)	
Discharge to another acute care hospital	8 (1.8)	2 (0.4)	5 (1.1)	
Discharged to nursing home	71 (16.2)	93 (20.9)	88 (19.3)	
Discharged home	236 (53.8)	227 (50.9)	235 (51.5)	
Other or unknown	13 (3.0)	13 (2.9)	18 (3.9)	
Serious adverse events — no. (%)¶	23 (5.2)	22 (4.9)	37 (8.1)	0.32



Protocol-based resuscitation of patients in whom septic shock was diagnosed in the ED did not improve outcomes

A Randomized Trial of Protocol-Based Care for Early Septic Shock

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Resuscitation and processes of care from baseline to 72h.

Intervention	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)	p-value ^a
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	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

A Randomized Trial of Protocol-Based Care for Early Septic Shock

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ProCESS Study
NEJM, May 1, 2014

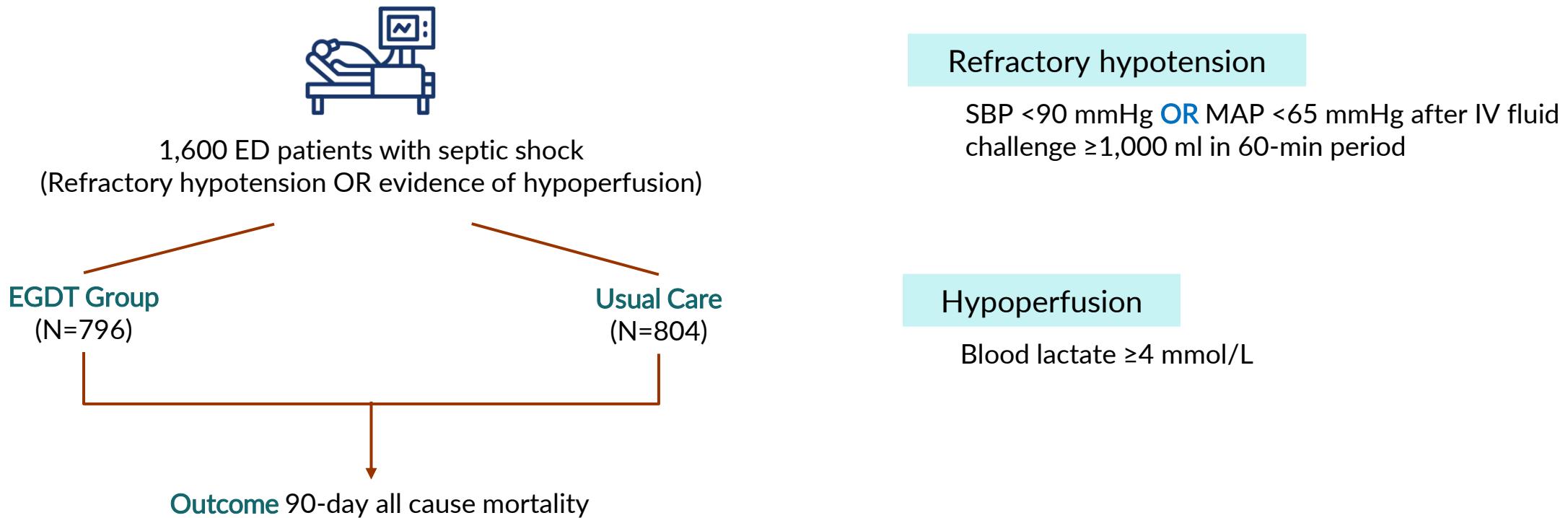


Intervention	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)	p-value ^g
Pre-randomization				
Intravenous fluids ^b – mL	2254 ± 1472	2226 ± 1363	2083 ± 1405	0.15
Fluids per body weight (mL/kg)	30.5 ± 22.3	29.2 ± 19.1	28 ± 21	
Vasopressor use ^c	84 (19.1)	75 (16.8)	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)	

3 ARISE Study

Goal-Directed Resuscitation for Patients with Early Septic Shock

ARISE Study
NEJM, Oct 16, 2014

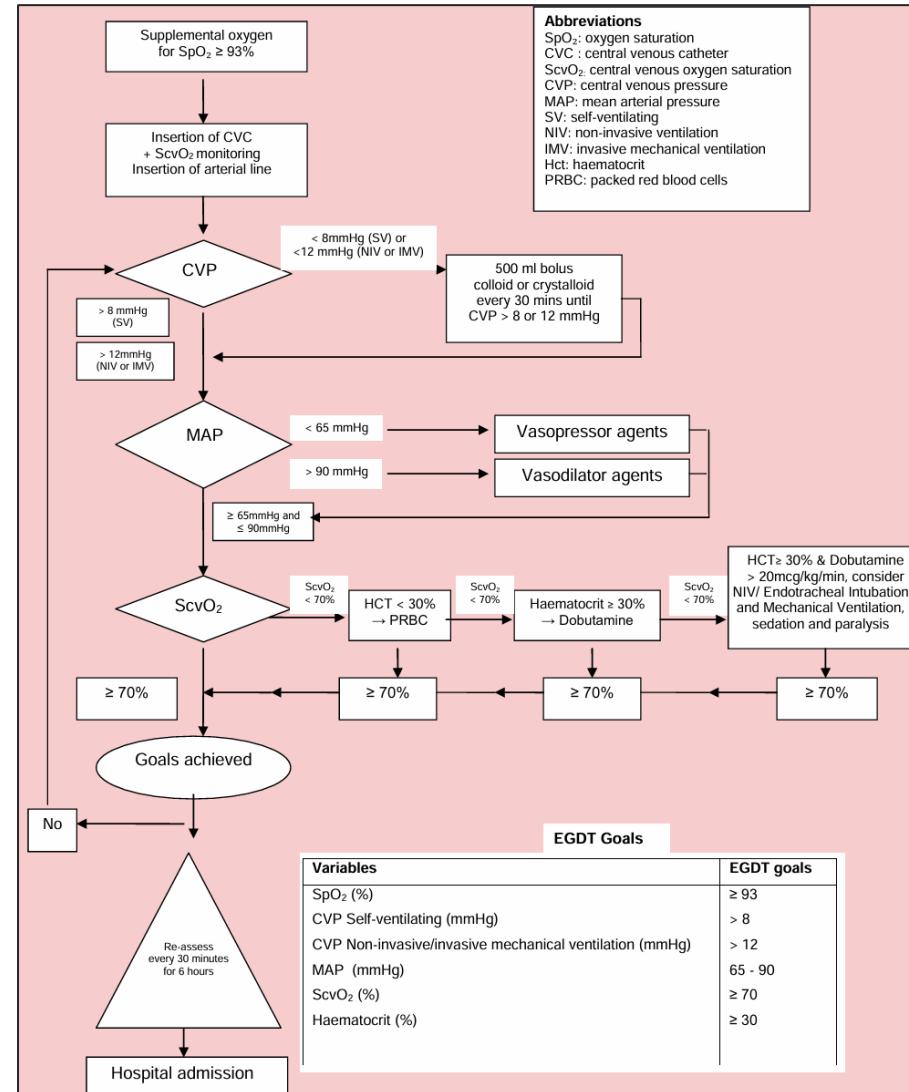


Goal-Directed Resuscitation for Patients with Early Septic Shock

ARISE Study
NEJM, Oct 16, 2014



Protocol for Early Goal-Directed Therapy



Goal-Directed Resuscitation for Patients with Early Septic Shock

ARISE Study
NEJM, Oct 16, 2014



Table 1. 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)

BASELINE CHARACTERISTICS

- Demographic and clinical characteristics at baseline were similar
- Total IV fluid before randomization = 2,500 ml (35 ml/kg)

Goal-Directed Resuscitation for Patients with Early Septic Shock

ARISE Study
NEJM, Oct 16, 2014



Table 2. Study Outcomes.

Variable	EGDT (N=793)	Usual Care (N=798)	Relative Risk (95% CI)	Risk Difference (95% CI)*	P Value
percentage points					
Primary outcome: death by day 90 — no./total no. (%)	147/792 (18.6)	150/796 (18.8)	0.98 (0.80 to 1.21)	-0.3 (-4.1 to 3.6)	0.90
Secondary outcomes					
Median duration of stay (IQR)†					
Emergency department — hr	1.4 (0.5–2.7)	2.0 (1.0–3.8)			<0.001
ICU — days	2.8 (1.4–5.1)	2.8 (1.5–5.7)			0.81
Hospital — days	8.2 (4.9–16.7)	8.5 (4.9–16.5)			0.89
Use and duration of organ support‡					
Invasive mechanical ventilation — no./total no. (%)	238/793 (30.0)	251/798 (31.5)	0.95 (0.82 to 1.11)	-1.4 (-6.0 to 3.1)	0.52
Median duration of invasive mechanical ventilation (IQR) — hr	62.2 (23.5–181.8)	65.5 (23.0–157.9)			0.28
Vasopressor support — no./total no. (%)	605/793 (76.3)	525/798 (65.8)	1.16 (1.09 to 1.24)	10.5 (6.1 to 14.9)	<0.001
Median duration of vasopressor support (IQR) — hr	29.4 (12.9–61.0)	34.2 (14.0–67.0)			0.24
Renal-replacement therapy — no./total no. (%)	106/793 (13.4)	108/798 (13.5)	0.99 (0.77 to 1.27)	-0.2 (-3.5 to 3.2)	0.94
Median duration of renal-replacement therapy (IQR) — hr§	57.8 (25.3–175.0)	85.9 (29.3–182.9)			0.40
Tertiary outcomes — no./total no. (%)					
Death by day 28	117/792 (14.8)	127/797 (15.9)	0.93 (0.73 to 1.17)	-1.2 (-4.7 to 2.4)	0.53
Death by the time of discharge from ICU	79/725 (10.9)	85/661 (12.9)	0.85 (0.64 to 1.13)	-2.0 (-5.4 to 1.5)	0.28
Death by the time of discharge from hospital¶	115/793 (14.5)	125/797 (15.7)	0.92 (0.73 to 1.17)	-1.2 (-4.7 to 2.3)	0.53

OUTCOMES

- No significant difference in 90-d all causes mortality

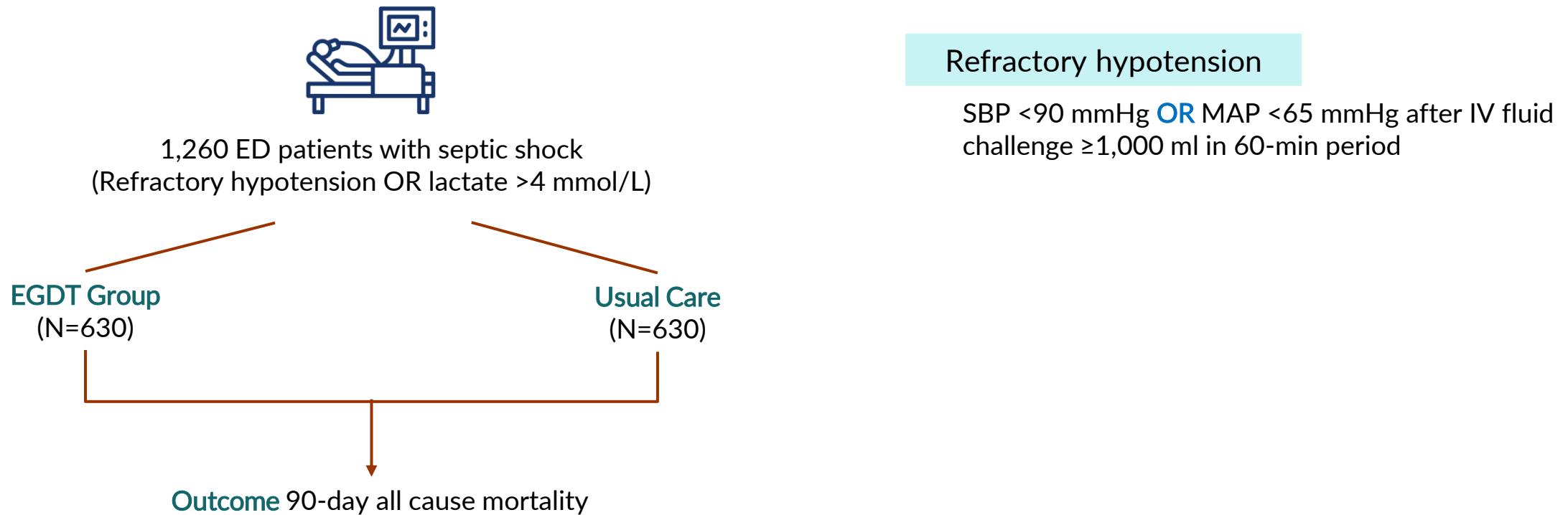
EGDT did not reduce all-cause mortality at 90 days

4

ProMISe Study

Trial of Early, Goal-Directed Resuscitation for Septic Shock

ProMISe Study
NEJM, Apr 2, 2015

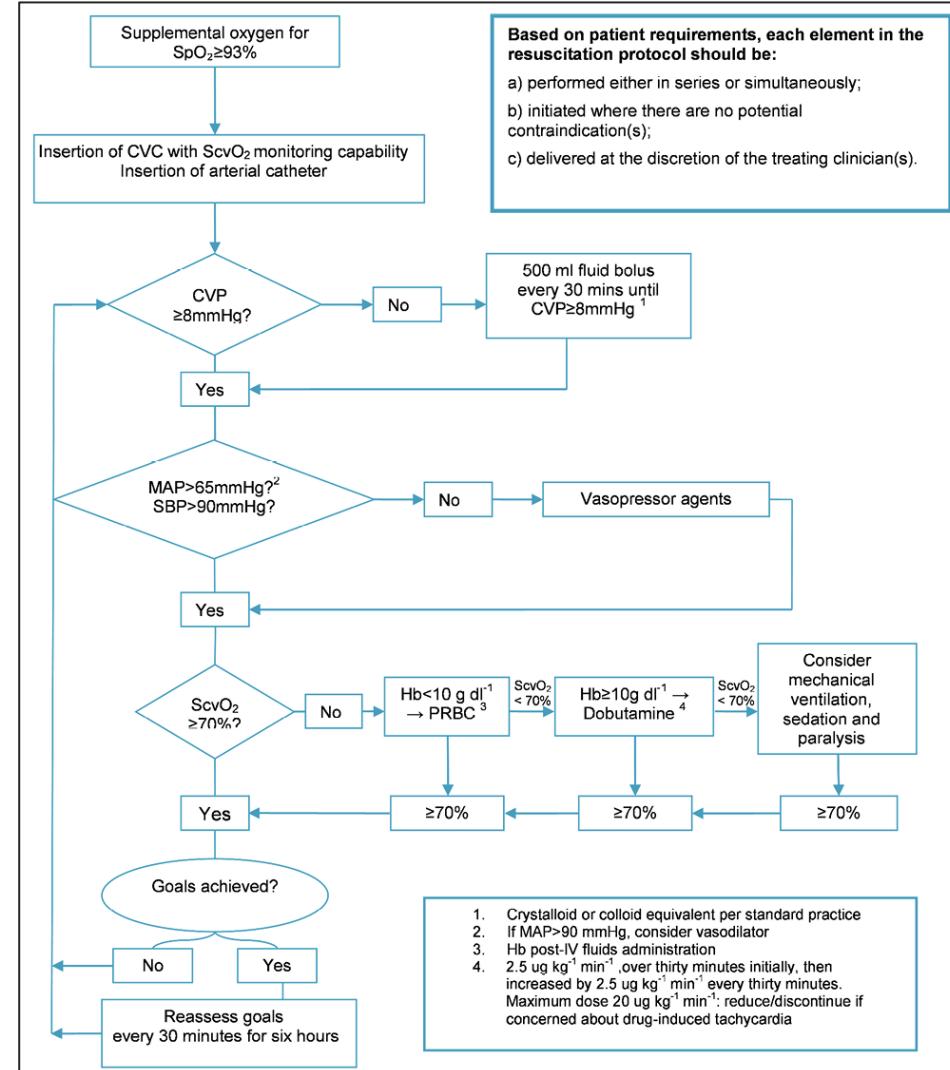


Trial of Early, Goal-Directed Resuscitation for Septic Shock

ProMISe Study
NEJM, Apr 2, 2015



Protocol for Early Goal-Directed Therapy



Trial of Early, Goal-Directed Resuscitation for Septic Shock

ProMISe Study
NEJM, Apr 2, 2015



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	EGDT (N=625)	Usual Care (N=626)
Age — yr	66.4±14.6	64.3±15.5
Male sex — no. (%)	356 (57.0)	367 (58.6)
Refractory hypotension — no. (%)	338 (54.1)	348 (55.6)
Systolic blood pressure — mm Hg	77.7±11.0	78.4±10.2
Mean arterial pressure — mm Hg	58.8±15.8	59.0±10.7
Hyperlactatemia — no. (%)	409 (65.4)	399 (63.7)
Blood lactate level — mmol/liter	7.0±3.5	6.8±3.2
Intravenous fluids administered†		
Before hospitalization until randomization — no./total no. (%)	612/625 (97.9)	606/625 (97.0)
Median total before hospitalization until randomization (IQR) — ml	1950 (1000–2500)	2000 (1000–2500)
Supplemental oxygen — no./total no. (%)‡	397/539 (73.7)	407/542 (75.1)
Median time from presentation in emergency department to randomization (IQR) — hr	2.5 (1.8–3.5)	2.5 (1.8–3.5)
Patient would have been admitted directly from emergency department to ICU if not enrolled in study		
Yes		
Patients — no. (%)	419 (67.0)	427 (68.2)
APACHE II score§	20±6.9	19.0±7.1
No		
Patients — no. (%)	206 (33.0)	199 (31.8)
APACHE II score§	15.0±6.1	15.8±6.5
APACHE II score§	18.7±7.1	18.0±7.1
MEDS score¶	8.0±3.4	7.9±3.3
SOFA score	4.2±2.4	4.3±2.4
Severe condition in medical history — no./total no. (%)**	181/622 (29.1)	161/626 (25.7)
Site of infection — no. (%)		
Lungs	228 (36.5)	207 (33.1)
Abdomen	40 (6.4)	51 (8.1)
Blood	97 (15.5)	86 (13.7)
Central nervous system	12 (1.9)	9 (1.4)
Soft tissue	39 (6.2)	39 (6.2)
Urinary tract	108 (17.3)	117 (18.7)
Other	21 (3.4)	37 (5.9)
No sepsis††	4 (0.6)	3 (0.5)
Unknown	76 (12.2)	77 (12.3)
Change from initial antimicrobial drugs by 72 hr — no./total no. (%)	359/615 (58.4)	342/617 (55.4)

BASELINE CHARACTERISTICS

- Demographic and clinical characteristics at baseline were similar
- Total IV fluid before randomization = 2,000 ml

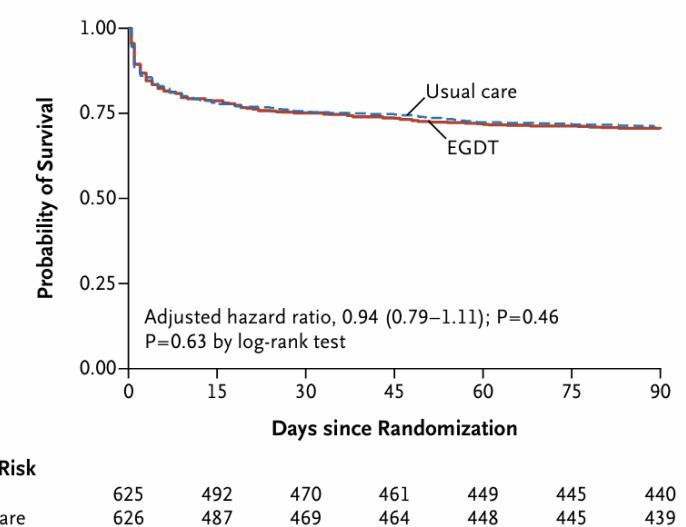
Trial of Early, Goal-Directed Resuscitation for Septic Shock

ProMISe Study
NEJM, Apr 2, 2015



Table 3. Study Outcomes.*

Outcome	EGDT (N=625)	Usual Care (N=626)	Incremental Effect (95% CI)	P Value
Clinical effectiveness				
Primary outcome: death from any cause at 90 days — no./total no. (%)	184/623 (29.5)	181/620 (29.2)		
Relative risk			1.01 (0.85 to 1.20)	0.90†
Absolute risk reduction — percentage points			-0.3 (-5.4 to 4.7)	
Unadjusted odds ratio			1.02 (0.80 to 1.30)	
Adjusted odds ratio			0.95 (0.74 to 1.24)	0.73
Secondary outcomes				
SOFA score‡				
At 6 hr	6.4±3.8	5.6±3.8	0.8 (0.5 to 1.1)§	<0.001
At 72 hr	4.0±3.8	3.7±3.6	0.4 (-0.0 to 0.8)§	0.056
Receipt of advanced cardiovascular support — no./total no. (%)	230/622 (37.0)	190/614 (30.9)	1.19 (1.02 to 1.40)¶	0.026†
Receipt of advanced respiratory support — no./total no. (%)	179/620 (28.9)	175/615 (28.5)	1.01 (0.85 to 1.21)¶	0.90†
Receipt of renal support — no./total no. (%)	88/620 (14.2)	81/614 (13.2)	1.08 (0.81 to 1.42)¶	0.62†
Days free from advanced cardiovascular support up to 28 days	20.3±11.9	20.6±11.8	-0.3 (-1.5 to 1.0)§	0.63
Days free from advanced respiratory support up to 28 days	19.6±12.1	19.8±12.0	-0.2 (-1.5 to 1.1)§	0.78
Days free from renal support up to 28 days	20.6±12.1	20.6±11.9	0.0 (-1.3 to 1.3)§	0.97
Median length of stay in emergency department (IQR) — hr	1.5 (0.4 to 3.1)	1.3 (0.4 to 2.9)		0.34
Median length of stay in ICU (IQR) — days	2.6 (1.0 to 5.8)	2.2 (0.0 to 5.3)		0.005
Median length of stay in hospital (IQR) — days	9 (4 to 21)	9 (4 to 18)		0.46
Death from any cause — no./total no. (%)				
At 28 days	155/625 (24.8)	152/621 (24.5)	1.01 (0.83 to 1.23)¶	0.90†
			0.95 (0.73 to 1.25)**	0.73
At hospital discharge	160/625 (25.6)	154/625 (24.6)	1.04 (0.86 to 1.26)¶	0.74†
			0.98 (0.75 to 1.29)**	0.90
Cost-effectiveness				
Health-related quality of life on EQ-5D at 90 days††	0.609±0.319	0.613±0.312	-0.004 (-0.051 to 0.044)§	0.88
Quality-adjusted life-yr up to 90 days	0.054±0.048	0.054±0.048	-0.001 (-0.006 to 0.005)§	0.85
Costs up to 90 days				0.26
Pounds	12,414±14,970	11,424±15,727	989 (-726 to 2,705)§	
Dollars	17,647±21,280	16,239±22,356	1,406 (-1,032 to 3,845)§	
Incremental net benefit up to 90 days‡‡				0.25
Pounds	NA	NA	-1,000 (-2,720 to 720)§	
Dollars	NA	NA	-1,422 (-3,866 to 1,023)§	
Serious adverse events — no. (%)	30 (4.8)	26 (4.2)	1.16 (0.69 to 1.93)¶	0.58†



OUTCOMES

- No significant difference in 90-d all causes mortality

Figure 2. Kaplan-Meier Survival Estimates.

Shown is the probability of survival for patients with severe sepsis receiving early, goal-directed therapy (EGDT) and those receiving usual care at 90 days.

Strict EGDT protocol did not lead to an improvement in outcome

Comparison of EGDT Studies

	Rivers et al	ProCESS	ARISE	ProMISe
Location	US	US	Australasia	UK
Population	263	1351	1600	1260
Sepsis Definition				
Suspected/Actual infection	Yes	Yes	Yes	Yes
SIRS criteria ≥2	Yes	Yes	Yes	Yes
Refractory ↓BP or lactate > 4 mmol/L	Yes	Yes	Yes	Yes

Comparison of EGDT Studies

	Rivers et al	ProCESS	ARISE	ProMISe
Protocol				
Fluid before randomization	20–30 ml/kg	~20–30 ml/kg Changed during study	1000 ml	1000 ml
Recruitment	Not specified	<12 h from ED arrival & <2 h from shock criteria	<6 h from ED arrival & <2 h from shock criteria	<6 h from ED arrival & <2 h from shock criteria
Intervention	EGDT 6 h	EGDT 6 h	EGDT 6 h	EGDT 6 h
Control	Usual therapy	1) Protocol usual therapy 2) Usual therapy	Usual therapy	Usual therapy

Comparison of EGDT Studies

	Rivers et al	ProCESS	ARISE	ProMISe
Primary Outcome				
Primary outcome	In-hospital mortality	60-day mortality	90-day mortality	90-day mortality
Intervention	30.5%	21.0%	18.6%	29.5%
Control	46.5%	1) 18.2% 2) 18.9%	18.8%	29.2%

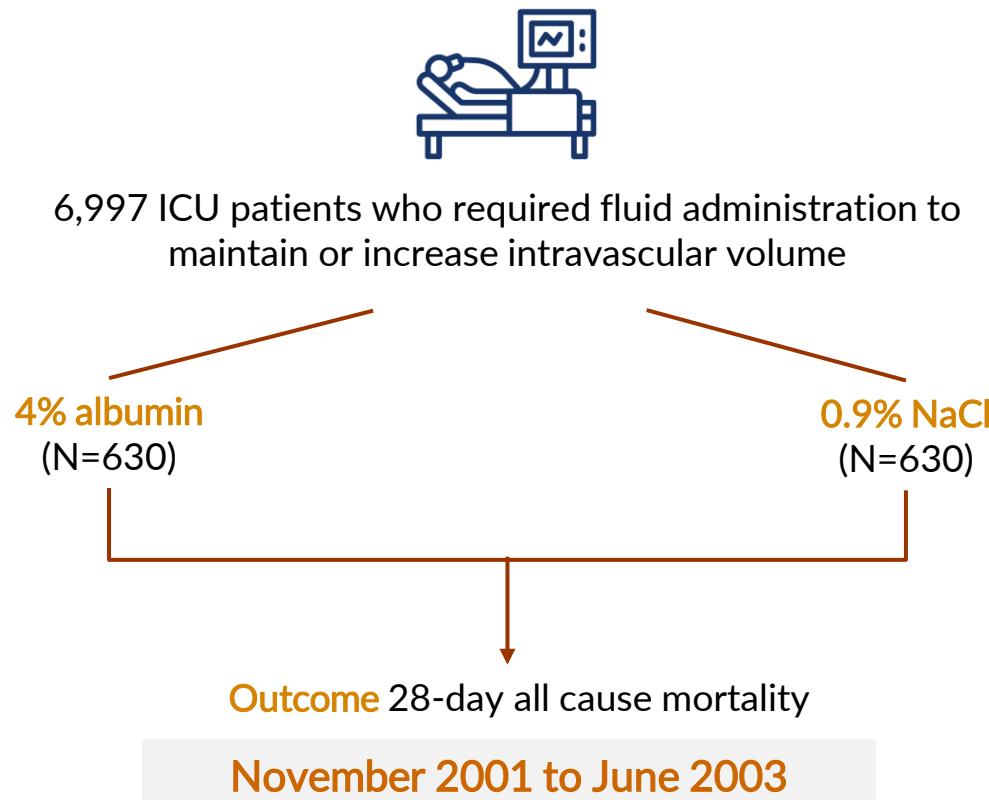
Crystalloid VS Colloid

1

SAFE Study

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

SAFE Study
NEJM, May 27, 2004



- Multicenter RCT
- The treating clinicians determined the amount and rate of fluid administration
- Maintenance fluids, specific replacement fluids, enteral or parenteral nutrition, and blood products at the discretion of the treating clinicians

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

SAFE Study
NEJM, May 27, 2004



Table 1. Baseline Characteristics of the Patients.*

Characteristic	Albumin Group	Saline Group
Age — yr	58.6±19.1	58.5±18.7
Female sex — no. (%)	1424 (40.7)	1376 (39.3)
Reason for admission to ICU — no. (%)		
Surgical	1473 (43.0)	1465 (42.8)
Medical	1955 (57.0)	1958 (57.2)
Source of admission to ICU — no. (%)		
Emergency department	948 (27.7)	977 (28.5)
Hospital floor	614 (17.9)	573 (16.7)
Another ICU	63 (1.8)	66 (1.9)
Another hospital	323 (9.4)	341 (10.0)
Operating room (emergency surgery)	801 (23.4)	780 (22.8)
Operating room (elective surgery)	662 (19.3)	678 (19.8)
Same ICU (readmission)	17 (0.5)	8 (0.2)
Predefined subgroups — no. (%)		
Trauma	597 (17.4)	590 (17.2)
Severe sepsis	603 (18.1)	615 (18.4)
Acute respiratory distress syndrome	61 (1.8)	66 (1.9)

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Albumin Group	Saline Group
APACHE II score†	18.7±7.9	19.0±8.0
Physiological variables		
Heart rate — beats/min	91.4±23.5	92.3±23.5
Mean arterial pressure — mm Hg	77.8±16.4	78.2±16.3
Central venous pressure — mm Hg	9.0±4.7	8.6±4.6‡
Urine output — ml/hr	89.7±132.4	95.0±161.4
Serum albumin — g/liter	27.4±7.8	27.7±7.9
Organ failure— no. (%)§		
No failure	1962 (57.2)	1885 (55.1)
1 organ	1075 (31.4)	1148 (33.5)
2 organs	335 (9.8)	329 (9.6)
3 organs	50 (1.5)	57 (1.7)
4 organs	5 (0.1)	4 (0.1)
5 organs	1 (<0.1)	0
Mechanical ventilation — no. (%)	2186 (63.8)	2217 (64.8)
Renal-replacement therapy — no. (%)	45 (1.3)	41 (1.2)
Albumin in previous 72 hr — no. (%)	127 (3.7)	135 (3.9)

BASELINE CHARACTERISTICS

- Severe sepsis ~18%
- Trauma ~17%
- Higher CVP in albumin group

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

SAFE Study
NEJM, May 27, 2004



Table 3. Primary and Secondary Outcomes.*

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	Absolute Difference (95% CI)	P Value
Status at 28 days — no./total no. (%)					
Dead	726/3473 (20.9)	729/3460 (21.1)	0.99 (0.91 to 1.09)		0.87
Alive in ICU	111/3473 (3.2)	87/3460 (2.5)	1.27 (0.96 to 1.68)		0.09
Alive in hospital†	793/3473 (22.8)	848/3460 (24.5)	0.93 (0.86 to 1.01)		0.10
Length of stay in ICU — days	6.5±6.6	6.2±6.2		0.24 (-0.06 to 0.54)	0.44
Length of stay in hospital — days†	15.3±9.6	15.6±9.6		-0.24 (-0.70 to 0.21)	0.30
Duration of mechanical ventilation — days	4.5±6.1	4.3±5.7		0.19 (-0.08 to 0.47)	0.74
Duration of renal-replacement therapy — days	0.48±2.28	0.39±2.0		0.09 (-0.0 to 0.19)	0.41
New organ failure — no. (%)‡					
No failure	1397 (52.7)	1424 (53.3)			0.85§
1 organ	795 (30.0)	796 (29.8)			
2 organs	369 (13.9)	361 (13.5)			
3 organs	68 (2.6)	75 (2.8)			
4 organs	18 (0.7)	17 (0.6)			
5 organs	2 (0.1)	0			
Death within 28 days according to subgroup — no./total no. (%)					
Patients with trauma	81/596 (13.6)	59/590 (10.0)	1.36 (0.99 to 1.86)		0.06
Patients with severe sepsis	185/603 (30.7)	217/615 (35.3)	0.87 (0.74 to 1.02)		0.09
Patients with acute respiratory distress syndrome	24/61 (39.3)	28/66 (42.4)	0.93 (0.61 to 1.41)		0.72

OUTCOMES

- No significant difference in 28-d mortality: 20.9% vs 21.1% (p=0.87)
- There was no difference in length of ICU stay, duration of mechanical ventilation or renal replacement therapy
- Albumin group received significantly less study fluid

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

SAFE Study
NEJM, May 27, 2004

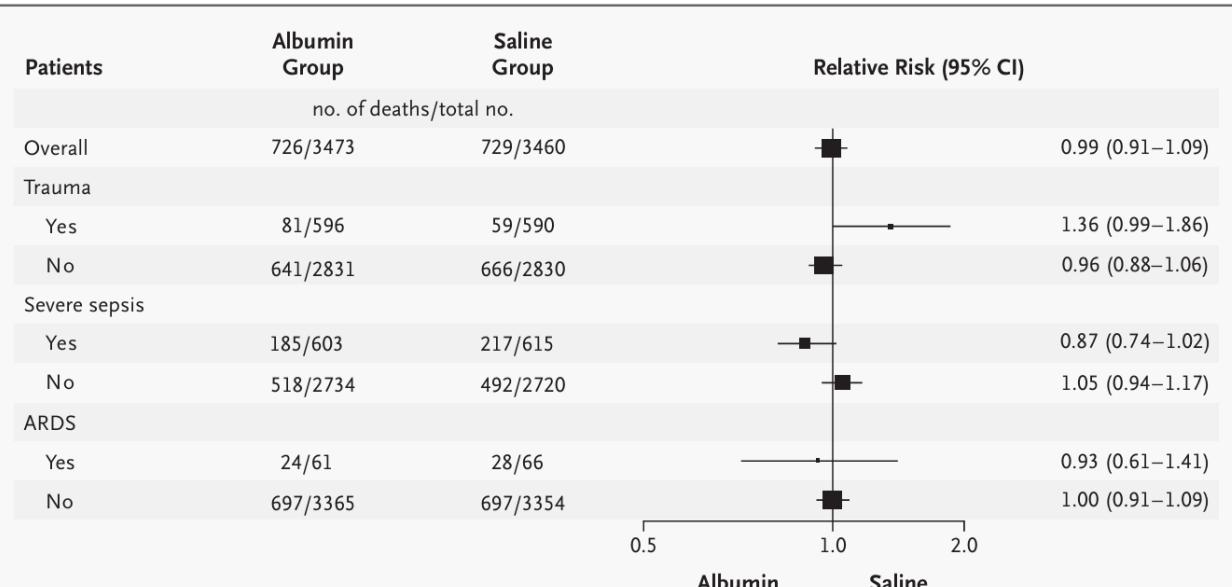


Figure 2. Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.

The size of each symbol indicates the relative number of events in the given group. The horizontal bars represent the confidence intervals (CI). ARDS denotes the acute respiratory distress syndrome.

SUBGROUP ANALYSIS

- No significant difference in 28-d mortality in patient with severe sepsis : 30.7% vs 35.3% ($p=0.09$)
- No significant difference in 28-d mortality in patient with trauma : 13.6% vs 10% ($p=0.06$)

POST HOC ANALYSIS

- **Albumin group has a higher 28-d mortality in patients with brain injury**

In ICU patients, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days

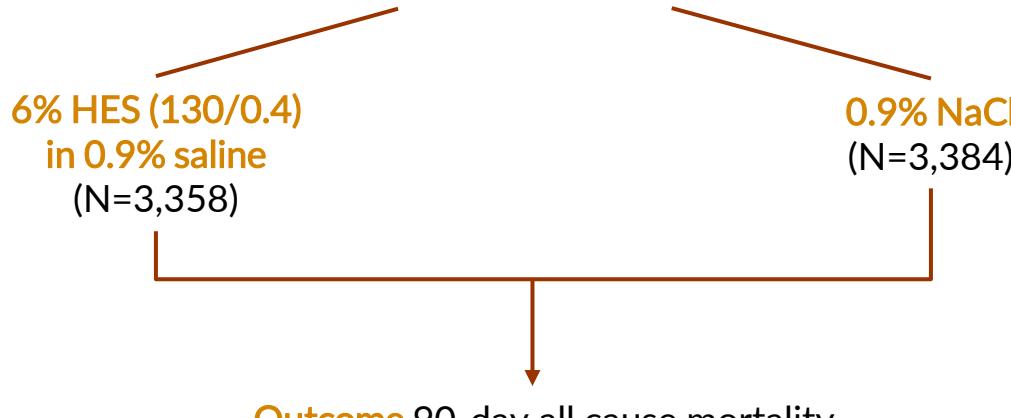
2 CHEST Study

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST Study
NEJM, Nov 15, 2012



6,742 ICU patients whom the treating clinician judged to require fluid resuscitation to correct hypovolemia



December 2009 to January 2012

- Multicenter, prospective, blinded, parallel-group, randomized, controlled trial
- 32 hospitals in Australia and New Zealand
- The treating clinicians determined the initial and subsequent volumes and the rate of administration of resuscitation fluid
- Study fluid was administered to a maximum dose of 50 ml/kg/day
- Followed by open-label 0.9% saline for the remainder of the 24-hour period

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST Study
NEJM, Nov 15, 2012



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	HES (N=3358)	Saline (N=3384)
Age — yr	63.1±17.0	62.9±16.9
Male sex — no./total no. (%)	2030/3356 (60.5)	2041/3384 (60.3)
Weight — kg	79.4±21.0	78.6±20.8
Source of admission to ICU — no./total no. (%)		
Emergency department	930/3353 (27.7)	931/3379 (27.6)
Hospital floor	659/3353 (19.7)	668/3379 (19.8)
Another ICU	53/3353 (1.6)	41/3379 (1.2)
Another hospital	315/3353 (9.4)	306/3379 (9.1)
Operating room		
After emergency surgery	625/3353 (18.6)	630/3379 (18.6)
After elective surgery	771/3353 (23.0)	803/3379 (23.8)
Diagnosis on admission — no./total no. (%)		
Surgical cases	1426/3353 (42.5)	1450/3379 (42.9)
Nonsurgical cases	1920/3353 (57.3)	1926/3379 (57.0)
APACHE II score — median (interquartile range)†	17.0 (12.0–22.0)	17.0 (12.0–23.0)
Time from ICU admission to randomization — hr	10.9±156.5	11.4±165.4

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	HES (N=3358)	Saline (N=3384)
Physiological variables		
Heart rate — beats/min	89.3±23.6	88.8±23.3
Mean arterial pressure — mm Hg	74.0±14.9	73.7±14.6
Central venous pressure — mm Hg	9.5±5.4	8.9±5.1
Lactate — mmol/liter	2.1±2.0	2.0±1.5
Mechanical ventilation — no./total no. (%)	2131/3326 (64.1)	2177/3354 (64.9)
Use of vasopressor — no./total no. (%)	1520/3337 (45.5)	1551/3361 (46.1)
Serum creatinine — µmol/liter	101.5±57.1	100.1±58.0
Urine output 6 hr before randomization — ml	453.5±418.3	426.6±422.9
Predefined subgroups — no./total no. (%)		
RIFLE criteria for acute kidney injury‡	522/1449 (36.0)	511/1421 (36.0)
Sepsis	979/3355 (29.2)	958/3376 (28.4)
Trauma	267/3358 (8.0)	265/3384 (7.8)
Traumatic brain injury	28/3338 (0.8)	30/3365 (0.9)
APACHE II score ≥25	597/3335 (17.9)	624/3356 (18.6)
Receipt of HES before randomization	509/3347 (15.2)	508/3372 (15.1)

BASELINE CHARACTERISTICS

- 2 groups had similar baseline characteristics
- Patients with AKI ~36%, sepsis ~29%, trauma ~8%

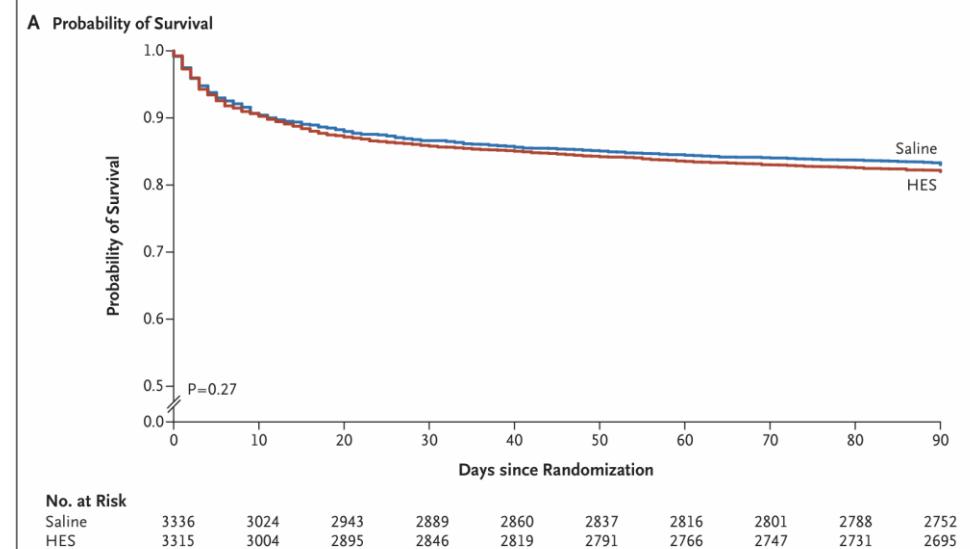
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST Study
NEJM, Nov 15, 2012



Table 2. Outcomes and Adverse Events.*

Variable	HES	Saline	Relative Risk (95% CI)	P Value
Outcome				
Primary outcome of death at day 90 — no./total no. (%)	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03
Tertiary outcomes — no./total no. (%)				
Death in ICU	364/3313 (11.0)	360/3331 (10.8)	1.02 (0.89 to 1.17)	0.81
Death within 28 days	458/3313 (13.8)	437/3331 (13.1)	1.05 (0.93 to 1.19)	0.40
Death in hospital	483/3307 (14.6)	456/3324 (13.7)	1.06 (0.95 to 1.20)	0.30
Mean Difference (95% CI)				
Service utilization — no.				
Days in ICU	7.3±0.2	6.9±0.2	0.4 (0.0 to 0.9)	0.07
Days in hospital	19.3±0.3	19.1±0.3	0.2 (-0.8 to 1.1)	0.72
Days receiving mechanical ventilation‡	6.0±0.2	5.7±0.2	0.4 (-0.1 to 0.8)	0.12
Days receiving renal-replacement therapy‡	5.6±0.4	5.5±0.4	0.1 (-0.1 to 1.2)	0.86
Treatment-related adverse events§				
Any event — no./total no. (%)	180/3871 (4.6)	95/2879 (3.3)		0.006
Pruritus	137/3871 (3.5)	73/2879 (2.5)		
Skin rash	34/3871 (0.9)	16/2879 (0.6)		
Other	9/3871 (0.2)	6/2879 (0.2)		
Serious adverse events — no./total no. ¶	2/3871 (0.1)	2/2879 (0.1)		0.77



OUTCOMES

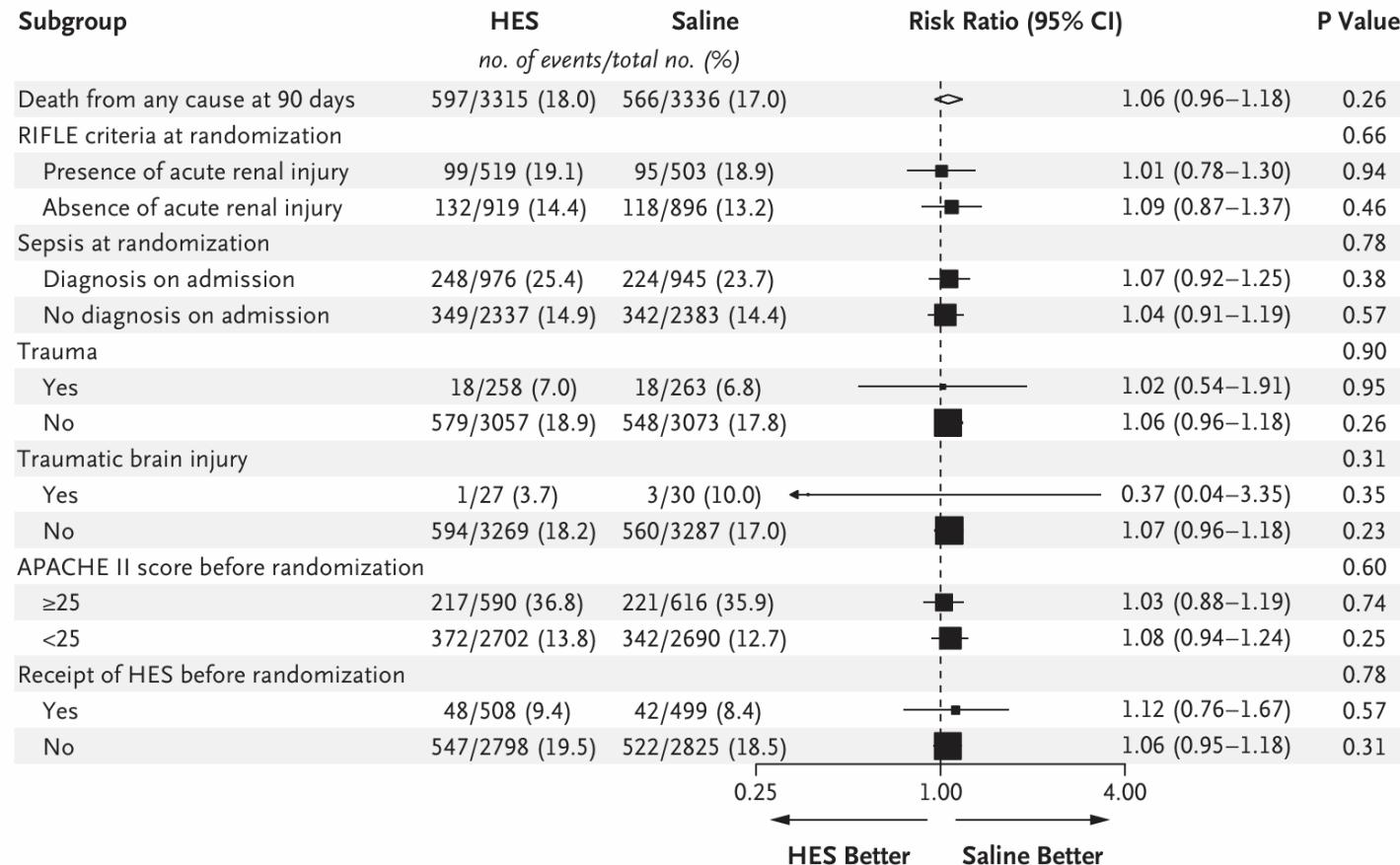
- No significant difference in 90-d all cause mortality: 18.0% vs 17.0% (RR 1.06, p=0.26)
- Rate of RRT and new hepatic organ failure was significantly higher in HES group
- No significant between-group difference in rates of death in the ICU, at 28 days, and in the hospital

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST Study
NEJM, Nov 15, 2012



B Subgroup Analyses



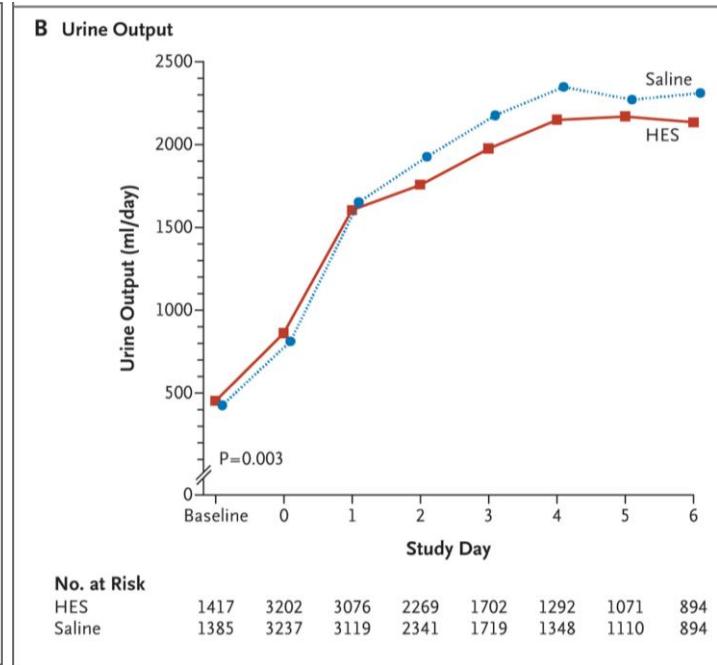
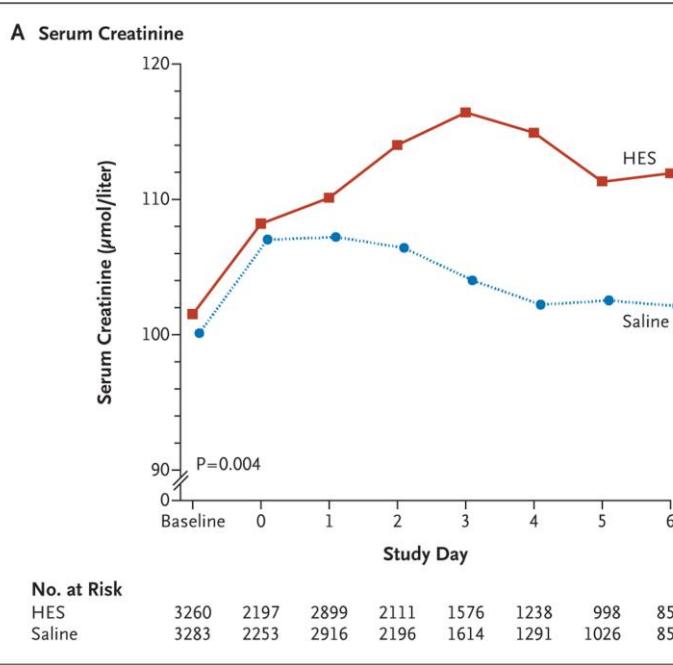
SUBGROUP ANALYSIS

- No significant heterogeneity in the effect of treatment on 90-day mortality in any subgroups

Figure 2. Probability of Survival and the Risk of Death at 90 Days, According to Subgroup.

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST Study
NEJM, Nov 15, 2012



POST HOC ANALYSIS

- Serum Cr levels were significantly increased and urine output was significantly decreased in the HES group during the first 7 days
- Risk of kidney dysfunction (RIFLE-R) or kidney injury (RIFLE-I) were higher in the HES group

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES or saline

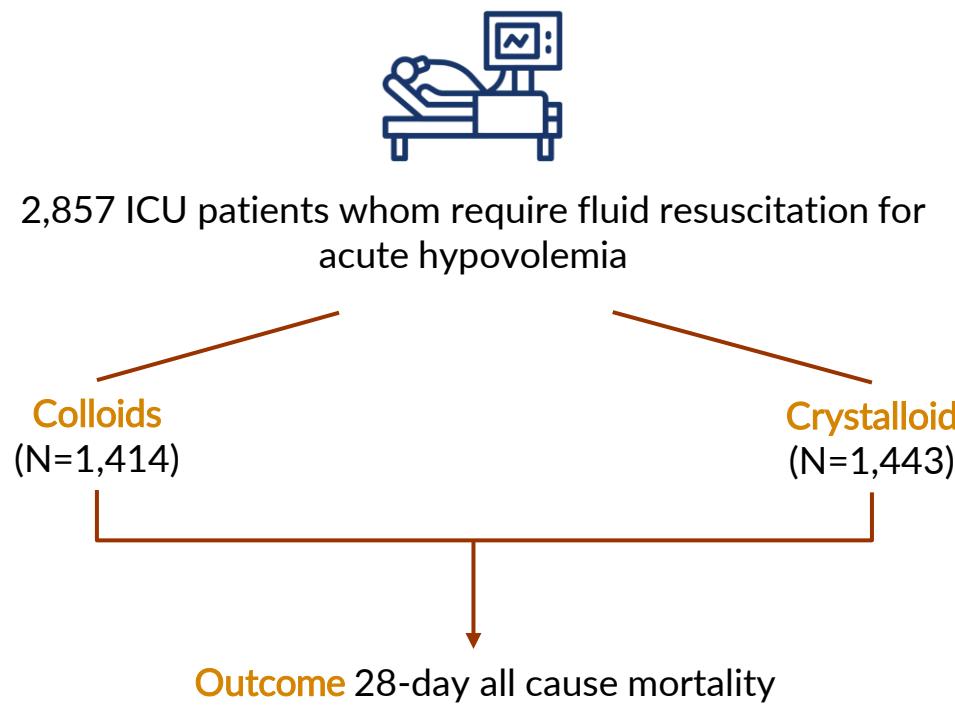
However, more patients who received resuscitation with HES were treated with renal-replacement therapy

3 CRISTAL Trial

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

CRISTAL Study
JAMA, Oct 9, 2013



February 2003 to August 2012

- International, multicenter, parallel-group, randomized, controlled trial
- 57 participating ICUs in France, Belgium, Canada, Algeria, and Tunisia
- The amount of fluid and duration of treatment was left at the discretion of the investigators
- Daily total dose of HES <30 ml/kg/day

Colloids

Either hypo-oncotic solutions (eg, gelatins, 4-5% albumin) or hyperoncotic solutions (eg, dextrans, HES, 20-25% albumin)

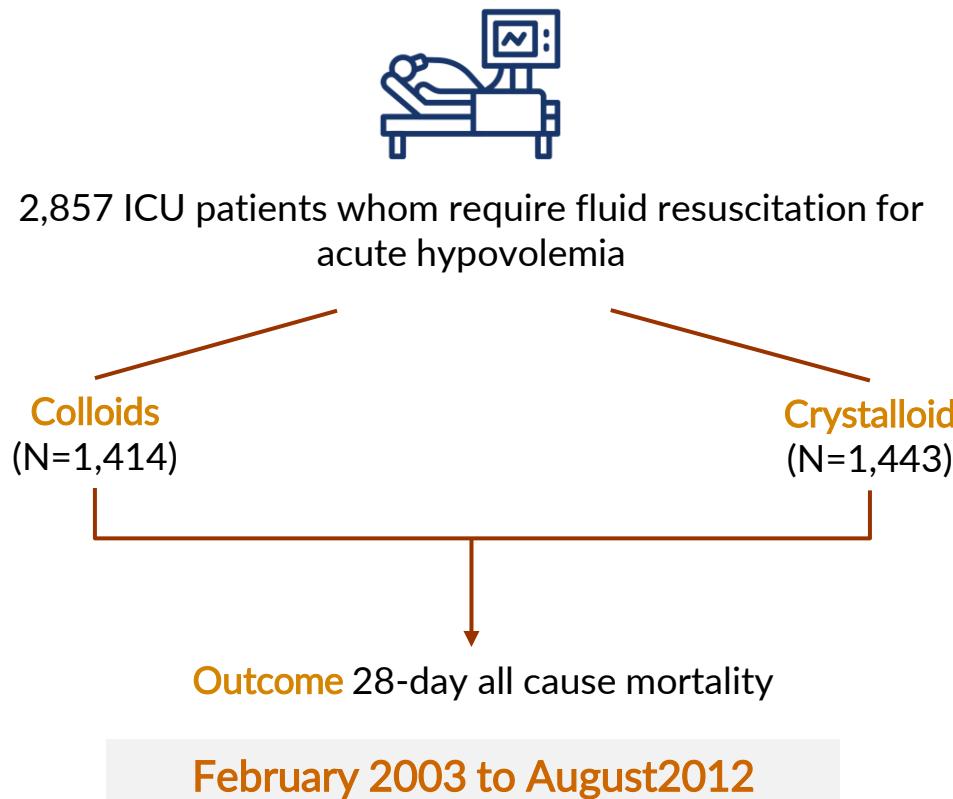
Crystalloids

Isotonic saline, hypertonic saline, or buffered solutions (eg, LR)

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

CRISTAL Study
JAMA, Oct 9, 2013



ACUTE HYPOVOLEMIA

Hypotension

SBP <90 mmHg, MAP <60 mmHg, orthostatic hypotension, or PPV >13%

Evidence of low filling pressure or low cardiac index

Assessed either invasively or non-invasively

Signs of tissue hypoperfusion or hypoxia

2 of following clinical symptoms

- Glasgow coma score <12
- Urine output <25 ml/h
- Mottled skin
- Capillary refilling time >3 sec

Arterial lactate >2 mmol/L, BUN >65 mg/dL, or FENa <1%

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

CRISTAL Study
JAMA, Oct 9, 2013



2,857 ICU patients whom require fluid resuscitation for acute hypovolemia

- Calculated 1,505 patients per group to detect an absolute difference of 5% in 28-day mortality with colloids

EARLY TERMINATION DURING 6TH INTERIM ANALYSIS



Outcome 28-day all cause mortality

February 2003 to August 2012

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

CRISTAL Study
JAMA, Oct 9, 2013



Table 1. Baseline Characteristics

	Colloids Group (n = 1414)	Crystalloids Group (n = 1443)
Age, median (IQR), y	63 (50-76)	63 (50-75)
Male sex, No. (%)	880 (62.2)	902 (62.5)
Weight, median (IQR), kg	70 (60-81)	70 (61-81)
Height, median (IQR), cm	170 (161-175)	169 (162-175)
Source of admission to ICU, No. (%)		
Community	674 (48.2)	745 (52.0)
Hospital ward	617 (44.1)	575 (40.1)
Other ICU	57 (4.1)	65 (4.5)
Long-term care facility	50 (3.6)	48 (3.3)
Type of ICU admission, No. (%)	(n = 1399)	(n = 1432)
Medical	991 (70.8)	1040 (72.6)
Emergency surgery	276 (19.7)	267 (18.6)
Scheduled surgery	109 (7.8)	89 (6.2)
Trauma	23 (1.6)	36 (2.5)
McCabe class, No. (%)		
No underlying disease or no fatal disease	903 (63.9)	913 (63.3)
Underlying ultimately fatal disease (>5 y)	429 (30.3)	469 (32.5)
Underlying rapidly fatal disease (<1 y)	82 (5.8)	61 (4.2)
Knaus disability scale, No. (%)		
Prior good health, no functional limitations	342 (24.5)	375 (26.3)
Mild to moderate limitation of activity because of chronic medical problem	439 (31.5)	446 (31.3)
Chronic disease producing serious but not incapacitating restriction of activity	323 (23.2)	325 (22.8)
Severe restriction of activity due to disease, includes persons bed-ridden or institutionalized due to illness	289 (20.8)	278 (19.5)

Table 1. Baseline Characteristics

	Colloids Group (n = 1414)	Crystalloids Group (n = 1443)
Physiology score, median (IQR)		
SAPS II ^a	48 (35-64)	50 (36-65)
SOFA ^b	8 (5-11)	8 (5-11)
Injury Severity ^c	(n = 79) 21 (14-27)	(n = 88) 22 (14-34)
Glasgow Coma Scale score, median (IQR)	(n = 1326) 11 (3-15)	(n = 1353) 11 (3-15)
Systolic blood pressure, median (IQR), mm Hg	(n = 1337) 92 (80-112)	(n = 1372) 94 (80-113)
Heart rate, median (IQR), beats/min	(n = 1335) 105 (86-123)	(n = 1366) 105 (88-21)
Urinary output, median (IQR), mL/h	(n = 1245) 40 (20-70)	(n = 1259) 40 (20-60)
Lactate levels, median (IQR), mmol/L	(n = 1151) 2.3 (1.3-3.8)	(n = 1176) 2.4 (1.4-4.5)
Fluid administration prior ICU admission (within the past 12 h)		
Crystalloids, No. (%)	526 (37.2)	402 (27.9)
Dose, median (IQR), mL	1000 (500-1000)	650 (500-1000)
Colloids, No. (%)	585 (41.4)	685 (47.5)
Dose, median (IQR), mL	1000 (500-2000)	1000 (500-2000)
Mechanical ventilation, No. (%)	1007 (71.2)	1061 (73.5)
Renal replacement therapy, No. (%)	67 (4.7)	73 (5.1)
Predefined strata, No. (%)		
Sepsis	774 (54.7)	779 (54.0)
Trauma	85 (6.0)	92 (6.4)
Hypovolemic shock (without sepsis or trauma)	555 (39.3)	572 (39.6)

BASELINE CHARACTERISTICS

- Severe sepsis was the main diagnosis

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

CRISTAL Study
JAMA, Oct 9, 2013



Table 2. Study Outcomes by Treatment Group

	Colloids (n = 1414)	Crystalloids (n = 1443)	RR (95% CI)	P Value ^a
Death				
Within 28 d	359 (25.4)	390 (27.0)	0.96 (0.88 to 1.04)	.26
Within 90 d	434 (30.7)	493 (34.2)	0.92 (0.86 to 0.99)	.03
In ICU	355 (25.1)	405 (28.1)	0.92 (0.85 to 1.00)	.06
In hospital	426 (30.1)	471 (32.6)	0.94 (0.87 to 1.02)	.07
No. of days alive and without the following treatment or condition	Mean (SD)	Mean Difference (95% CI)		
Mechanical ventilation within the first 7 d	2.1 (2.4)	1.8 (2.3)	0.30 (0.09 to 0.48)	.01
Mechanical ventilation within the first 28 d	14.6 (11.4)	13.5 (11.5)	1.10 (0.14 to 2.06)	.01
Renal replacement therapy within the first 7 d	4.8 (2.9)	4.6 (2.9)	0.2 (-0.4 to 0.8)	.99
Renal replacement therapy within the first 28 d	13.9 (11.3)	13.1 (11.4)	0.8 (-1.6 to 3.3)	.90
Organ failure (SOFA score <6) within the first 7 d	6.2 (1.8)	6.1 (1.8)	0.06 (-0.10 to 0.20)	.31
Organ failure (SOFA score <6) within the first 28 d	21.4 (10.3)	20.9 (10.6)	0.6 (-0.4 to 1.5)	.16
Vasopressor therapy within the first 7 d	5.0 (3.0)	4.7 (3.1)	0.30 (-0.03 to 0.50)	.04
Vasopressor therapy within the first 28 d	16.2 (11.5)	15.2 (11.7)	1.04 (-0.04 to 2.10)	.03
ICU stay within the first 28 d	8.3 (9.0)	8.1 (9.2)	0.2 (-0.5 to 0.9)	.69
Hospital stay within the first 28 d	11.9 (11.1)	11.6 (11.4)	0.3 (-0.5 to 1.1)	.37

	Colloids Group (n=1414)		Crystalloids Group (n=1443)		HR (95% CI)	Favors Colloids	Favors Crystalloids
Reason for ICU Admission	No. of Patients	No. of Deaths	No. of Patients	No. of Deaths			
Other causes of hypovolemic shock	555	131	572	152	0.87 (0.69-1.10)	-	-
Sepsis	774	215	779	226	0.95 (0.78-1.10)	-	-
Trauma	85	13	92	12	1.19 (0.54-2.60)	-	-
All patients	1414	359	1443	390	0.93 (0.80-1.10)	-	-

Forest plot showing HR (95% CI) for all patients. The diamond represents the overall estimate, and the horizontal line at 1.0 represents the null effect.

OUTCOMES

- No significant difference in 28-d all cause mortality: 25.4% vs 27.0% (RR 0.96, p=0.26)
- Lower 90-d mortality rate in colloid group
- No difference in rate of RRT
- Higher no. of days alive and without mechanical ventilation and vasopressor therapy in colloid group

SUBGROUP ANALYSIS

- No significant heterogeneity in the effect of treatment on mortality in any of the predefined strata at 28 days

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

CRISTAL Study
JAMA, Oct 9, 2013



Table 4. Mortality Outcomes in Patients With Sepsis

	Colloids Group, No.		Crystalloids Group, No.		HR (95% CI)
	Patients	Deaths	Patients	Deaths	
28-d Mortality					
Entire population	774	215	779	226	0.95 (0.78-1.14)
HES vs isotonic saline	375	105	557	157	0.97 (0.76-1.25)
Gelatins vs isotonic saline	152	40	557	157	0.90 (0.63-1.27)
HES vs Ringer solution	375	105	37	12	0.84 (0.46-1.53)
Gelatins vs Ringer solution	152	40	37	12	0.77 (0.40-1.47)
Albumin vs isotonic saline	59	19	557	157	1.16 (0.72-1.87)
90-d Mortality					
Entire population	774	252	779	286	0.87 (0.73-1.03)
HES vs isotonic saline	375	120	557	197	0.89 (0.71-1.11)
Gelatins vs isotonic saline	152	47	557	197	0.84 (0.61-1.16)
HES vs Ringer solution	375	120	37	16	0.71 (0.42-1.20)
Gelatins vs Ringer solution	152	47	37	16	0.67 (0.38-1.18)
Albumin vs isotonic saline	59	22	557	197	1.07 (0.69-1.67)

OUTCOMES

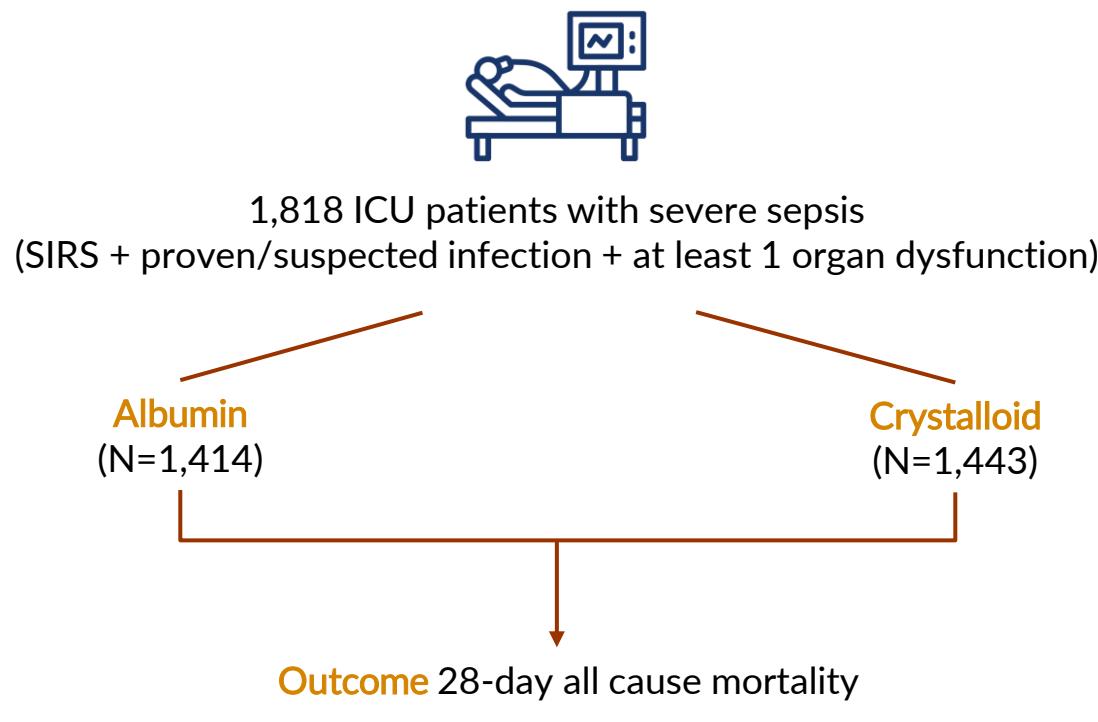
- Estimated treatment effects were not markedly modified when considering fluid subsets

Among ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality

4 ALBIOS Trial

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

ALBIOS Study
NEJM, Apr 10, 2014



- Multicenter, open-label, randomized, controlled trial
- 100 ICUs in Italy
- During resuscitation phase, fluids were administered in both groups according to EGDT
- Crystalloids were administered whenever it was clinically indicated by the attending physician

Albumin Group

Albumin + crystalloid

- Administer 20% albumin 300 ml to maintain a serum albumin level ≥ 30 g/L

Crystalloid Group

Crystalloid solution alone

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

ALBIOS Study
NEJM, Apr 10, 2014



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Albumin Group (N=903)	Crystalloid Group (N=907)
Age — yr		
Median	70	69
Interquartile range	57–77	59–77
Female sex — no. (%)	360 (39.9)	357 (39.4)
Body-mass index†	27±6	27±6
Reason for ICU admission — no. (%)		
Medical	511 (56.6)	518 (57.1)
Elective surgery	69 (7.6)	58 (6.4)
Emergency surgery	323 (35.8)	331 (36.5)
Preexisting condition — no. (%)‡		
Liver disease	13 (1.4)	14 (1.5)
COPD	113 (12.5)	108 (11.9)
Chronic renal failure	44 (4.9)	32 (3.5)
Immunodeficiency	115 (12.7)	128 (14.1)
Congestive or ischemic heart disease	149 (16.5)	165 (18.2)
SAPS II score§		
Median	48	48
Interquartile range	37–59	37–60
Physiological variable¶		
Heart rate — beats/min	105±22	106±20
Mean arterial pressure — mm Hg	74±16	73±15
Central venous pressure — mm Hg	10.0±4.9	9.8±4.7
Urine output — ml/hr		
Median	50	50
Interquartile range	20–100	25–100

Table 1. Characteristics of the Patients at Baseline.*

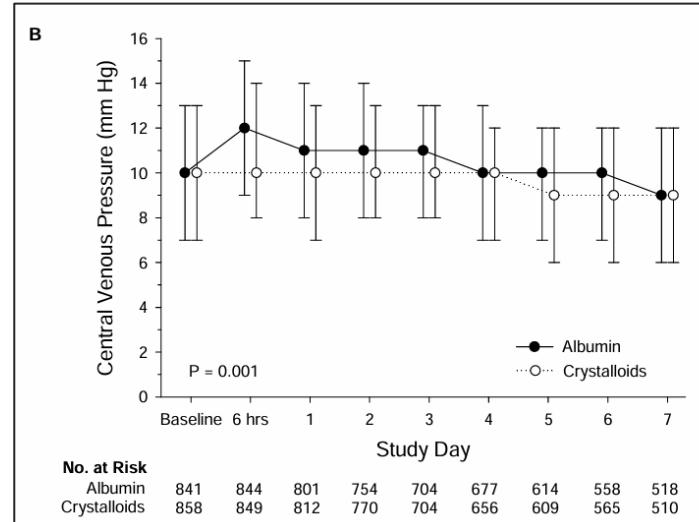
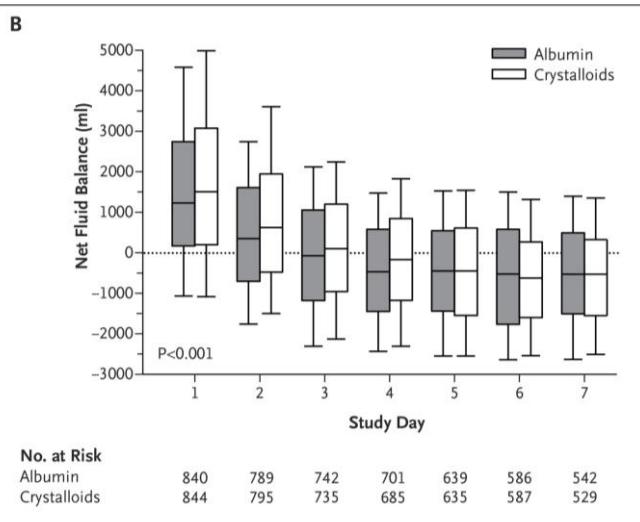
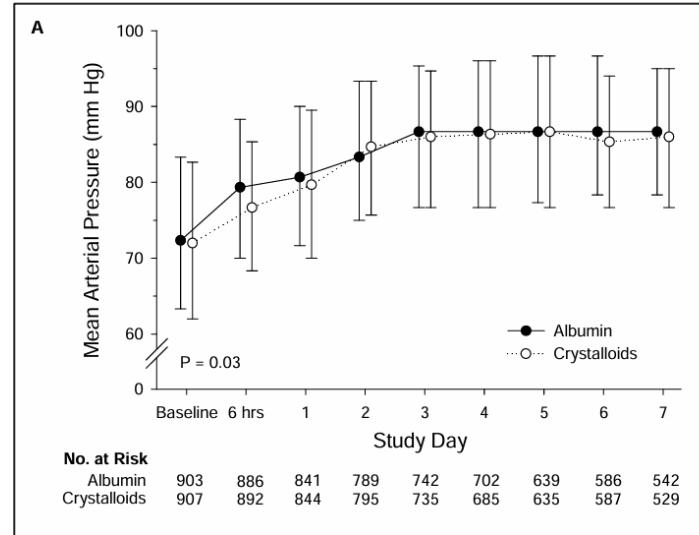
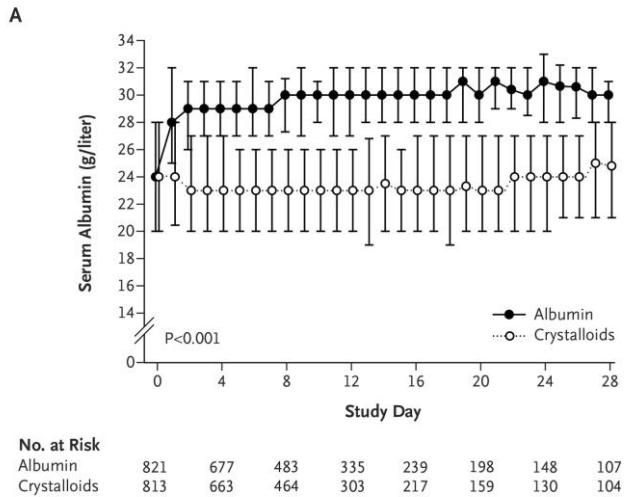
Characteristic	Albumin Group (N=903)	Crystalloid Group (N=907)
Lactate — mmol/liter		
Median	2.3	2.5
Interquartile range	1.4–4.2	1.6–4.3
Serum albumin — g/liter	24.1±6.3	24.2±6.2
Hemoglobin — g/dl	10.9±2.1	11.0±2.0
Central venous oxygen saturation — %		
Median	73	73
Interquartile range	65–79	68–80
SOFA score		
Median	8	8
Interquartile range	6–10	5–10
Organ dysfunction — no. (%)**		
1 organ	188 (20.8)	208 (22.9)
2 organs	361 (40.0)	303 (33.4)
3 organs	236 (26.1)	248 (27.3)
4 organs	89 (9.9)	115 (12.7)
5 organs	29 (3.2)	33 (3.6)
Shock — no. (%)††	565 (62.6)	570 (62.8)
Mechanical ventilation — no. (%)	709 (78.5)	737 (81.3)
Fluid administration in previous 24 hr — no. (%)		
Albumin	153 (16.9)	176 (19.4)
Synthetic colloids	452 (50.1)	479 (52.8)

BASELINE CHARACTERISTICS

- Slight imbalance in the number of patients with organ dysfunction and values of central venous oxygen saturation

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

ALBIOS Study
NEJM, Apr 10, 2014



RESULTS

- Serum albumin level was significantly higher in the albumin group
- Daily net fluid balances were lower in the albumin group
- During the first 7 days, patients in the albumin group had a significantly lower heart rate & significantly higher mean arterial pressure

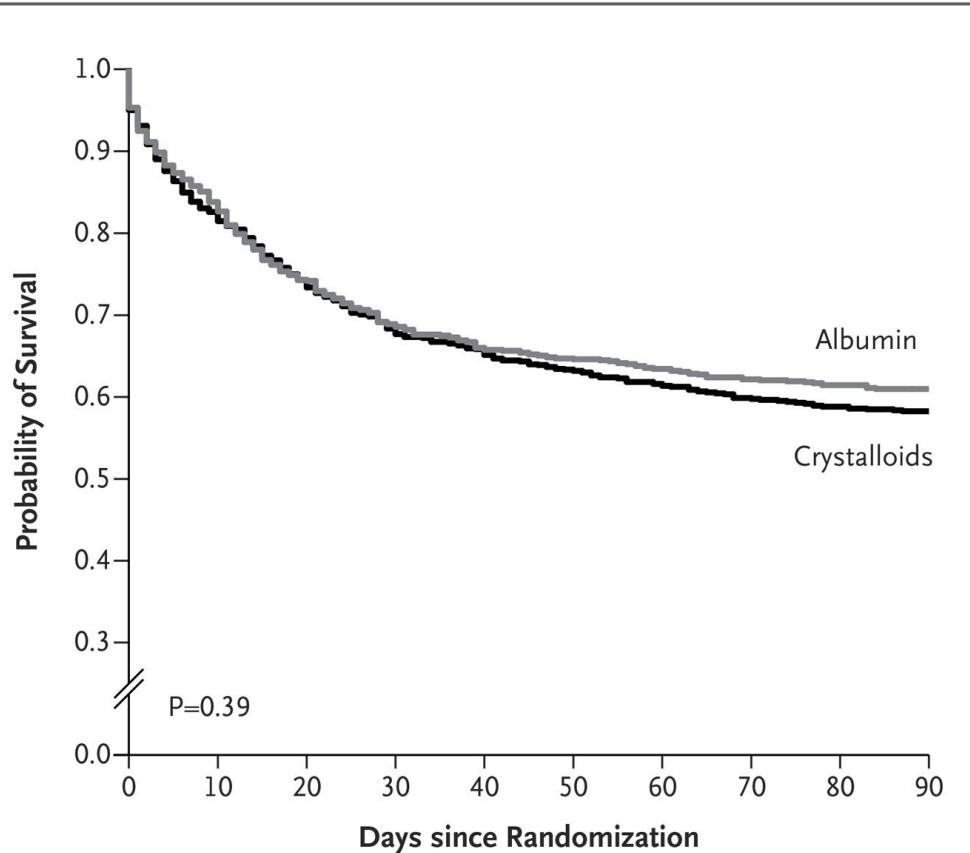
Albumin Replacement in Patients with Severe Sepsis or Septic Shock

ALBIOS Study
NEJM, Apr 10, 2014



OUTCOMES

- Mortality at 28 days was not different between groups
31.8% vs 32.0% (RR 1.0, p 0.94)



No. at Risk

Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

ALBIOS Study
NEJM, Apr 10, 2014



Table 2. Outcomes.

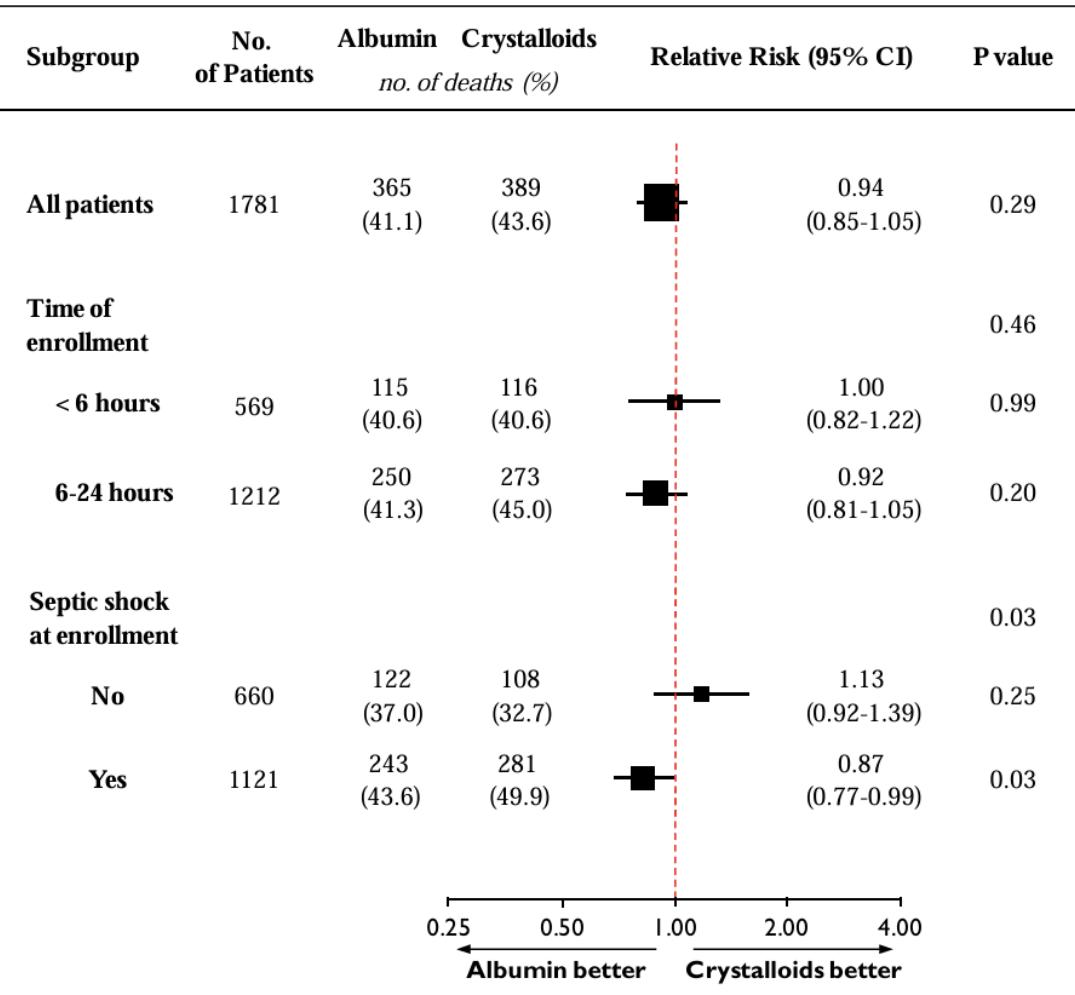
Outcome	Albumin Group	Crystallloid Group	Relative Risk (95% CI)	P Value
Primary outcome: death at 28 days — no./total no. (%)	285/895 (31.8)	288/900 (32.0)	1.00 (0.87–1.14)	0.94
Secondary outcomes				
Death at 90 days — no./total no. (%)	365/888 (41.1)	389/893 (43.6)	0.94 (0.85–1.05)	0.29
New organ failures — no./total no. (%)*				0.99
None	372/836 (44.5)	383/841 (45.5)		
1 organ	283/836 (33.9)	287/841 (34.1)		
2 organs	130/836 (15.6)	123/841 (14.6)		
3 organs	40/836 (4.8)	36/841 (4.3)		
4 organs	10/836 (1.2)	11/841 (1.3)		
5 organs	1/836 (0.1)	1/841 (0.1)		
SOFA score†				0.23
Median	6.00	5.62		
Interquartile range	4.00–8.50	3.92–8.28		
SOFA subscore†				
Cardiovascular				0.03
Median	1.20	1.42		
Interquartile range	0.46–2.31	0.60–2.50		
Respiratory				0.63
Median	2.00	2.00		
Interquartile range	1.56–2.48	1.57–2.50		
Renal				0.15
Median	0.83	0.75		
Interquartile range	0.14–2.14	0.07–2.00		
Coagulation				0.04
Median	0.64	0.50		
Interquartile range	0.00–1.62	0.00–1.59		
Liver				0.02
Median	0.28	0.20		
Interquartile range	0.00–1.00	0.00–0.92		
Length of stay — days				
In ICU				0.42
Median	9	9		
Interquartile range	4–18	4–17		
In hospital‡				0.65
Median	20	20		
Interquartile range	10–36	9–38		

OUTCOMES

- No significant difference in 90-d mortality
- No significant difference in either the number of newly developed organ failures or the median SOFA score
- SOFA score for each organ: Albumin group had
 - Lower cardiovascular score ($P = 0.03$)
 - Higher coagulation score ($P = 0.04$)
 - Higher liver score ($P = 0.02$)

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

ALBIOS Study
NEJM, Apr 10, 2014



POST HOC ANALYSIS

- Albumin group had significant lower rate of 90-d mortality in patients with septic shock: 43.6% vs 49.9% (RR 0.87, p=0.03)

In patients with severe sepsis, albumin replacement in addition to crystalloids, did not improve the rate of survival at 28 and 90 days

Comparison of Type of Fluid Studies

	SAFE	CHEST	CRISTAL	ALBIOS
Location	Australia	Australia & New Zealand	France, Belgium & Canada	Italy
Population	6997	6742	2857	1818
Protocol				
Patients	ICU patients (Sepsis 18%)	ICU patients (Sepsis 29%)	ICU patients (Sepsis 54%)	Severe sepsis only
Intervention (colloid)	4% albumin	6% HES Max 50 ml/kg/d	Colloid Max HES 30 ml/kg/d	20% albumin Keep albumin >30 g/L
Control (crystalloid)	0.9% NaCl	0.9% NaCl	Crystalloid	Crystalloid

Comparison of Type of Fluid Studies

	SAFE	CHEST	CRISTAL	ALBIOS
Primary Outcome				
Primary outcome	28-day mortality	90-day mortality	28-day mortality	28-day mortality
Intervention	20.9%	18.0%	25.4%	31.8%
Control	21.1%	17.0%	27.0%	32.0%
Other Outcomes				
	Albumin group had higher mortality in TBI patients	More AKI, RRT, and hepatic failure in HES	No different in RRT	Albumin group had significant hemodynamic advantages

Type of Crystalloid

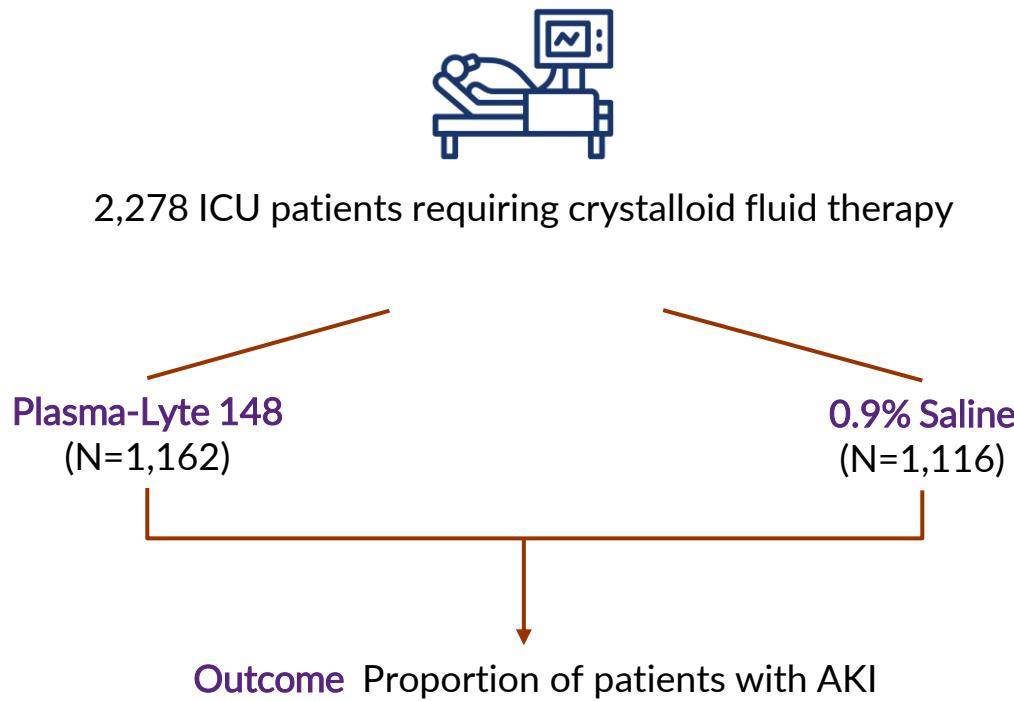
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SPLIT Trial

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

SPLIT Trial
JAMA, Nov 3, 2015



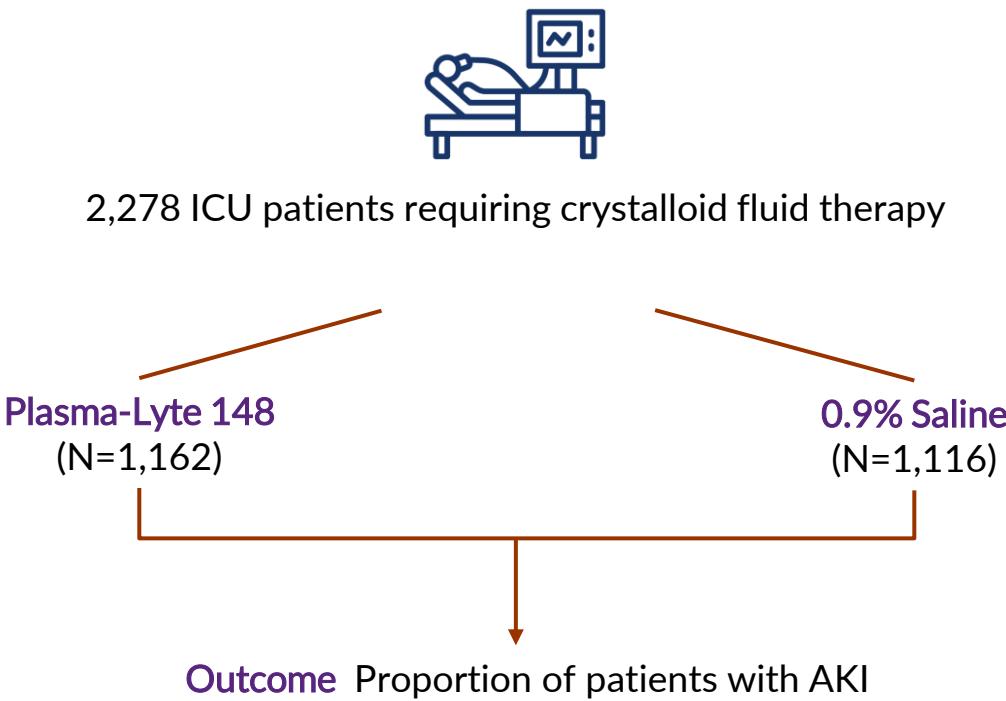
- Hypothesis: high chloride content of saline contributes to the development of AKI
- Prospective, multicenter, blinded, cluster-randomized, double crossover study
- 4 tertiary ICUs in New Zealand
- 2 commercially available buffered crystalloid solutions: Hartmann solution and Plasma-Lyte 148 (PL-148)
 - PL-148 was used more commonly
- The treating clinician determined the rate and frequency of fluid administration
- Definition of AKI based on RIFLE criteria

April 2014 to October 2014

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

SPLIT Trial
JAMA, Nov 3, 2015



Plasma-Lyte	0.9% Saline
Na+ 140	Na + 154
Cl- 98	Cl- 154
K+ 5	K+ 0
Ca++ 0	Ca++ 0
Mg++ 3	Mg++ 0
Lactate 0	Lactate 0
Acetate 27	Acetate 0
Gluconate 23	Gluconate 0
OSMO 280 mOsm/L	OSMO 308 mOsm/L

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

SPLIT Trial
JAMA, Nov 3, 2015



Table 1. Characteristics of the Patients at Baseline

Characteristic	No. (%)	
	Buffered Crystalloid (n = 1152)	Saline (n = 1110)
Age, mean (SD), y	60.10 (16.79)	60.95 (16.25)
Men	739 (64)	746 (67)
Weight, mean (SD), kg	80.4 (20.1)	80.7 (20.0)
Ethnicity		
New Zealand European	749 (65)	723 (65)
Maori	116 (10)	110 (10)
Pacific Island peoples	90 (8)	91 (8)
Other	197 (17)	186 (17)
Comorbidities		
Chronic respiratory disease	27 (2)	30 (3)
Chronic cardiovascular disease	12 (1)	23 (2)
Leukemia/myeloma	9 (1)	7 (1)
Immunosuppression by disease	17 (1)	12 (1)
Immunosuppression by therapy	46 (4)	50 (5)
Hepatic failure	5 (<1)	7 (1)
Cirrhosis	8 (1)	12 (1)
Lymphoma	14 (1)	5 (<1)
AIDS	1 (<1)	1 (<1)
Metastatic cancer	25 (2)	31 (3)

Table 1. Characteristics of the Patients at Baseline

Characteristic	No. (%)	
	Buffered Crystalloid (n = 1152)	Saline (n = 1110)
Source of admission to ICU		
Operating room	822 (71)	798 (72)
After elective surgery	650 (56)	642 (58)
After emergency surgery	172 (15)	156 (14)
Emergency department	168 (15)	148 (13)
Hospital floor	87 (8)	88 (8)
Another hospital (excluding from another ICU)	43 (4)	47 (4)
Another ICU	32 (3)	29 (3)
Operative admission diagnoses ^a	822 (71)	798 (72)
Cardiovascular	560 (49)	548 (49)
Gastrointestinal	98 (9)	87 (8)
Gynecological	6 (1)	11 (1)
Neurological	38 (3)	35 (3)
Musculoskeletal / skin	18 (2)	13 (1)
Renal	17 (1)	23 (2)
Respiratory	48 (4)	59 (5)
Trauma	17 (1)	7 (1)
Other postoperative	20 (2)	15 (1)

Table 1. Characteristics of the Patients at Baseline

Characteristic	No. (%)	
	Buffered Crystalloid (n = 1152)	Saline (n = 1110)
Nonoperative admission diagnoses ^a	330 (29)	312 (28)
Respiratory	70 (6)	59 (5)
Cardiovascular	54 (5)	52 (5)
Neurological	47 (4)	50 (5)
Sepsis	41 (4)	43 (4)
Metabolic	40 (3)	23 (2)
Trauma	40 (3)	61 (5)
Gastrointestinal	18 (2)	12 (1)
Renal	4 (<1)	0
Musculoskeletal/skin	1 (<1)	3 (<1)
Hematological	0	1 (<1)
Other medical diseases	15 (1)	8 (1)
APACHE II score, mean (SD) ^b	14.1 (6.9)	14.1 (6.7)
Mechanical ventilation	768 (67)	731 (66)
Serum creatinine, mg/dL		
Baseline (before illness), mean (SD)	0.98 (0.76)	0.99 (0.68)
No. of patients	1133	1092
Most recent, mean (SD)	1.18 (1.00)	1.15 (1.15)
No. of patients	847	820
Time from ICU admission to first fluid, median (IQR), h	1.17 (0.22-3.80)	1.25 (0.17-3.50)

BASELINE CHARACTERISTICS

- Similar in both groups
- High proportion of post elective surgery: 56% and 58%

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

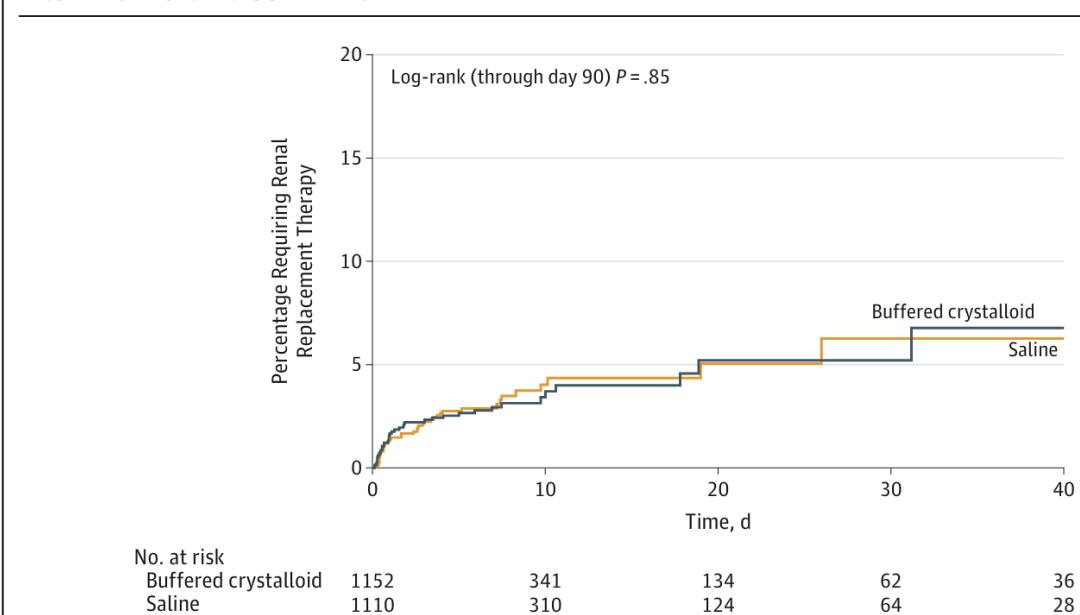
SPLIT Trial
JAMA, Nov 3, 2015



Table 2. Outcomes for Patients in the Intensive Care Unit Receiving Buffered Crystalloid vs Saline Fluid Therapy

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 2.05)	.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	

Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial



OUTCOMES

- No statistical difference in proportion of patients with AKI based on RIFLE criteria within 90 days: 9.6% vs 9.2% (p=0.77)
- No significant difference in the probability of requiring RRT

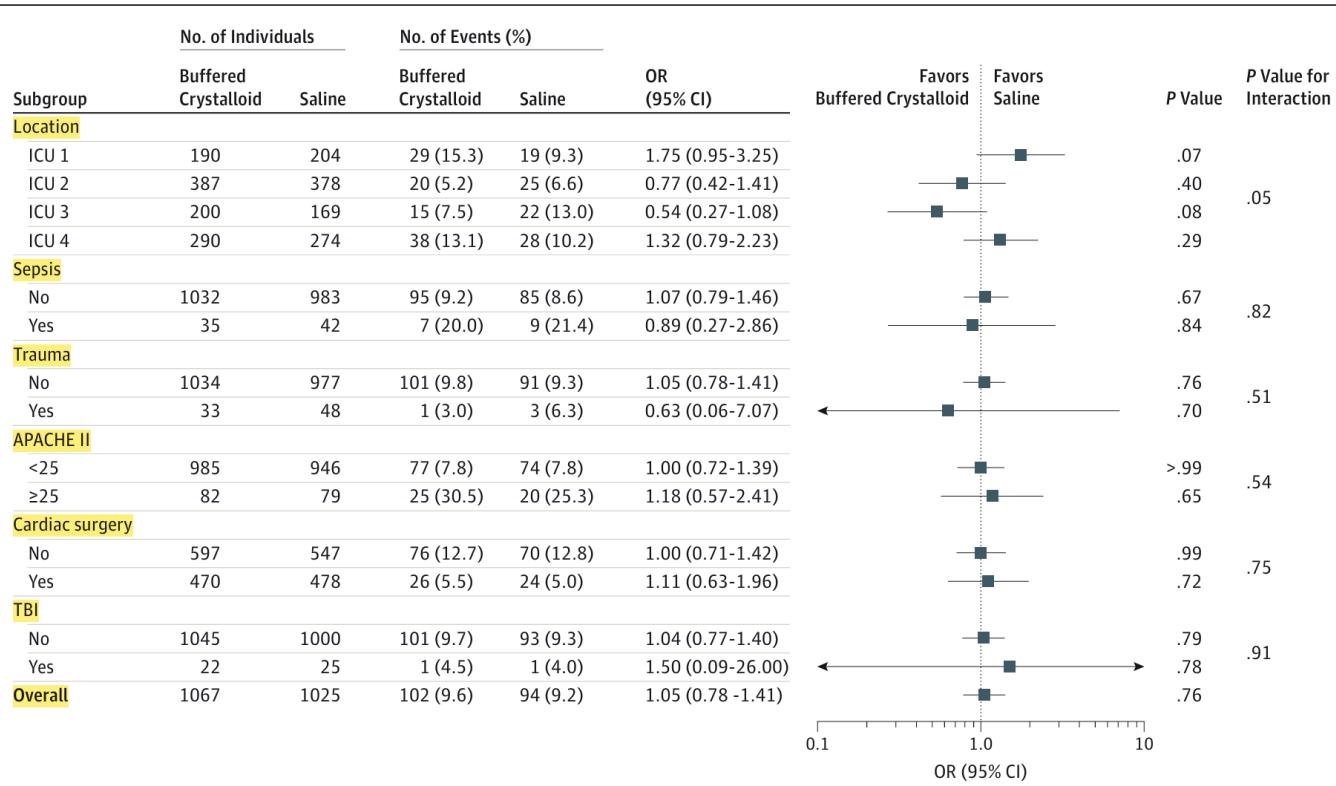
Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

SPLIT Trial
JAMA, Nov 3, 2015



Figure 3. Risk of Acute Kidney Injury by Subgroup for Patients Admitted to the Intensive Care Unit Receiving Buffered Crystalloid vs Saline Fluid Therapy



OUTCOME

- No significant between-group difference in Δcreatinine, daily serum creatinine to day 7, service utilization, and 90-d mortality

SUBGROUP ANALYSIS

- No significant heterogeneity in the effect of treatment on AKI or failure in any of the predefined subgroups

Among patients receiving crystalloid fluid therapy in the ICU, use of a *buffered crystalloid did not reduce the risk of AKI*

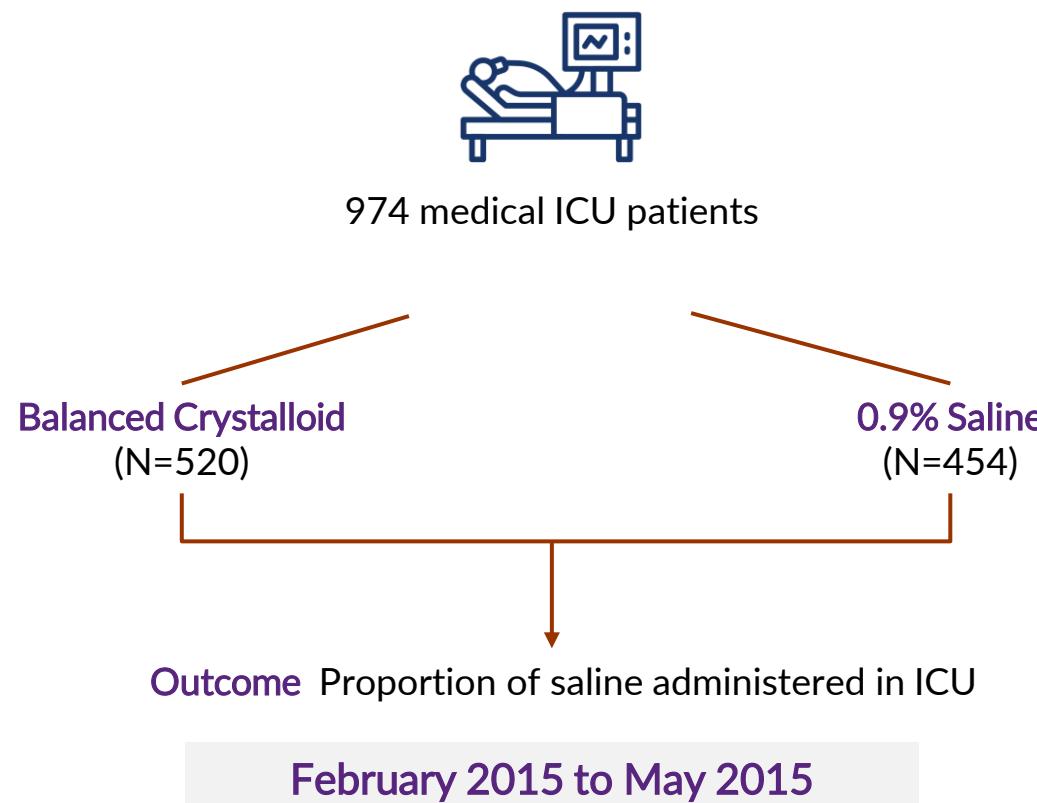
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SALT Trial = Pilot Study

Balanced Crystalloids versus Saline in the Intensive Care Unit

The SALT Randomized Trial

SALT Trial
AJRCCM, May 15, 2017



- To pilot a cluster-randomized, multiple-crossover trial using software tools within the electronic health record to compare saline to balanced crystalloids
- The crystalloid used during the first month of the study was selected by computer-generated simple randomization
- Thereafter, the crystalloid assigned to the ICU alternated monthly for the duration of the study
- Decisions regarding frequency, rate, total volume, and additive content of the crystalloids were made by the treating clinician

Balanced Crystalloid

lactated Ringer's solution or Plasma-Lyte A

Balanced Crystalloids versus Saline in the Intensive Care Unit

The SALT Randomized Trial

SALT Trial
AJRCCM, May 15, 2017



Patient Characteristics	Saline (n = 454)	Balanced (n = 520)
Age, median (IQR), yr	58 (46–70)	57 (44–68)
Men, n (%)	246 (54.2)	268 (51.5)
White, n (%)	358 (78.9)	376 (72.3)
Weight, median (IQR), kg	77.6 (63.0–95.3)	77.1 (63.5–95.3)
Body mass index, median (IQR), kg/m ²	26.4 (22.4–32.8)	26.7 (22.5–32.5)
Renal comorbidities, n (%)		
Chronic kidney disease, stage III or greater*	104 (22.9)	119 (22.9)
Previous renal replacement therapy receipt	44 (9.7)	42 (8.1)
Source of admission to ICU, n (%)		
Emergency department	256 (56.4)	310 (59.6)
Transfer from another hospital	93 (20.5)	106 (20.4)
Hospital ward	80 (17.6)	79 (15.2)
Another ICU within the hospital	15 (3.3)	14 (2.7)
Operating room	6 (1.3)	4 (0.8)
Outpatient	4 (0.9)	7 (1.3)
Admitting diagnosis, n (%)		
Sepsis or septic shock	130 (28.6)	130 (25.0)
Respiratory failure	53 (11.7)	41 (7.9)
Gastrointestinal bleeding	25 (5.5)	19 (3.7)
Liver failure	21 (4.6)	24 (4.6)
Ingestion	22 (4.8)	32 (6.2)
Malignancy	19 (4.2)	27 (5.2)
Diabetic ketoacidosis	20 (4.4)	21 (4.0)
Pneumonia	14 (3.1)	16 (3.1)
Acute kidney injury	5 (1.1)	18 (3.5)
Other	115 (25.3)	150 (28.8)
Mechanical ventilation, n (%)	155 (34.1)	174 (33.5)
Vasopressors, n (%)	111 (24.4)	114 (21.9)
UHC expected mortality, mean (95% CI), % [†]	14.7 (12.7–16.7)	13.1 (11.4–14.9)
Serum creatinine, median (IQR), mg/dl		
Lowest in 12 mo before hospitalization	0.78 (0.64–1.10)	0.76 (0.62–1.05)
n (%) of patients	271 (59.7)	324 (62.3)
Lowest between hospitalization and ICU admission	0.97 (0.76–1.51)	0.95 (0.75–1.61)
n (%) of patients	122 (26.9)	137 (26.3)
Estimated by three-variable formula [‡]	0.91 (0.88–0.96)	0.91 (0.88–0.95)
n (%) of patients	61 (13.4)	59 (11.3)
Study baseline	0.86 (0.69–1.12)	0.83 (0.67–1.09)
Acute kidney injury, stage II or greater [§]	87 (19.2)	96 (18.5)

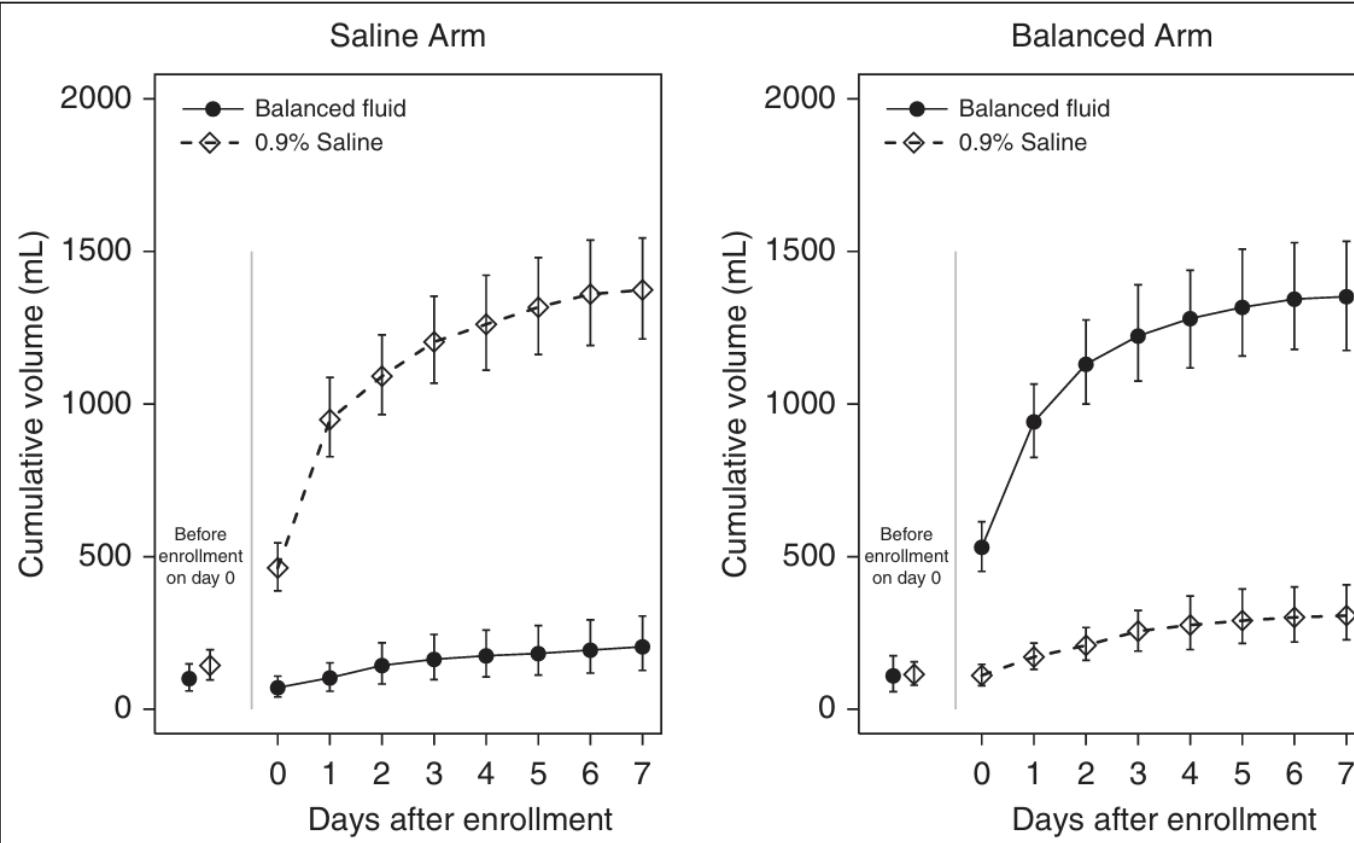
BASELINE CHARACTERISTICS

- Patients in 2 groups were similar at baseline
- Most were admitted from the ED
- Sepsis and respiratory failure were the most common admitting diagnoses

Balanced Crystalloids versus Saline in the Intensive Care Unit

The SALT Randomized Trial

SALT Trial
AJRCCM, May 15, 2017



FLUID THERAPY

- Saline made up 91.2% of the isotonic crystalloid given in the ICU to patients in the saline arm compared with 21.2% in the balanced arm
- Patients in both group received a similar total volume of intravenous crystalloid by 7 and 30 days
 - *7 days*: median volume 1,250 ml in saline arm vs 1,320 ml in balanced arm
 - *30 days*: median volume 1,424 ml in saline arm vs 1,617 ml in balanced arm

Balanced Crystalloids versus Saline in the Intensive Care Unit

The SALT Randomized Trial

SALT Trial
AJRCCM, May 15, 2017



Outcome	n	Saline (n = 454)	Balanced (n = 520)	P Value
Secondary outcome				
Major adverse kidney event within 30 d, n (%)*	974	112 (24.7)	128 (24.6)	0.98
Additional clinical outcomes				
In-hospital mortality, n (%)				
Before ICU discharge	974	44 (9.7)	45 (8.7)	0.57
Before 30 d	974	68 (15.0)	72 (13.8)	0.62
Before 60 d	974	83 (18.3)	87 (16.7)	0.53
ICU-free days, median (IQR)	969	25.1 (22.1 to 26.2)	25.2 (21.8 to 26.4)	0.58
Mean ± SD		21.0 ± 9.3	21.1 ± 9.1	
Ventilator-free days, median (IQR)	974	28.0 (25.0 to 28.0)	28.0 (26.0 to 28.0)	0.85
Mean ± SD		22.9 ± 9.9	23.2 ± 9.6	
Vasopressor-free days, median (IQR)	974	28.0 (27.0 to 28.0)	28.0 (27.0 – 28.0)	0.78
Mean ± SD		23.5 ± 9.9	23.9 ± 9.6	
Renal replacement therapy-free days, median (IQR)	974	28.0 (28.0 to 28.0)	28.0 (28.0 to 28.0)	0.42
Mean ± SD		23.7 ± 10.0	24.0 ± 9.7	
Additional renal outcomes				
Serum creatinine, mg/dl				
Highest before discharge or day 30, median (IQR), mg/dl	950	1.19 (0.81 to 2.30)	1.19 (0.80 to 2.62)	0.51
Change from baseline to highest value, median (IQR), mg/dl	950	0.07 (-0.10 to 0.50)	0.07 (-0.10 to 0.50)	0.65
Final value before discharge or 30 d, median (IQR), mg/dl	950	0.89 (0.69 to 1.54)	0.87 (0.70 to 1.45)	0.90
Among survivors, median (IQR), mg/dl	808	0.85 (0.68 to 1.40)	0.82 (0.69 to 1.30)	0.48
Final creatinine >200% baseline, n (%)	974	59 (13.0)	76 (14.6)	0.47
Among survivors to hospital discharge	834	42 (10.9)	46 (10.3)	0.71
Among survivors to hospital discharge without new RRT	814	39 (10.2)	41 (9.5)	0.39
Acute kidney injury, stage II or greater, n (%)†	974	129 (28.4)	135 (26.0)	0.39
Developing after enrollment‡	974	87 (19.2)	97 (18.7)	0.84
Receipt of new renal replacement therapy, n (%)	974	14 (3.1)	24 (4.6)	0.22
Duration of in-hospital receipt, median (IQR), d	38	5.5 (3.0 to 8.2)	3.0 (0.5 – to 4.5)	0.04
Continued receipt after hospital discharge, n (%)	38	2 (0.4)	5 (1.0)	0.68

OUTCOME

- The highest serum chloride between enrollment and day 30 was greater in the saline group : 109 mmol/L vs 108 mmol/L (p=0.03)
- Incidence of stage II or greater AKI by KDIGO creatinine criteria did not differ between groups
- New RRT was similar between groups
- Proportion of patients who experienced MAKE30 was similar
 - Among patients who received larger volumes, those assigned to the saline group experienced a higher incidence of MAKE30

An electronic health record-embedded, cluster-randomized, multiple-crossover trial comparing saline with balanced crystalloids can produce well-balanced study groups and separation in crystalloid receipt

3

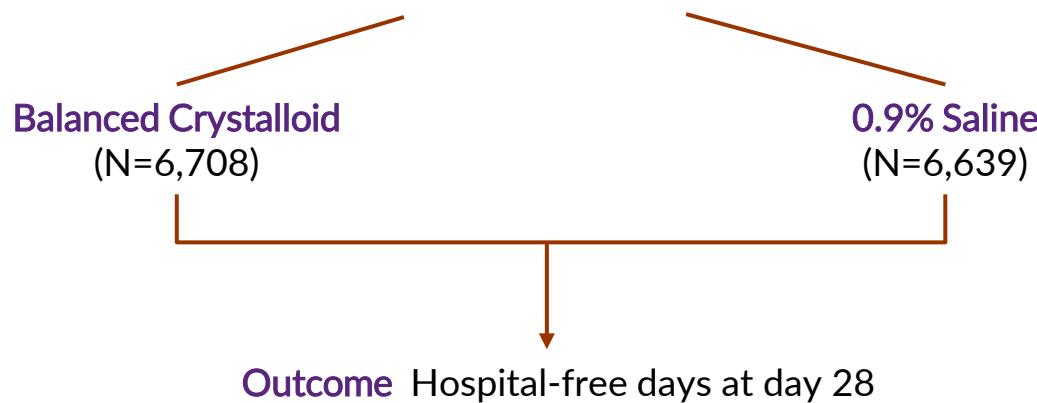
SALT-ED Trial

Balanced Crystalloids versus Saline in Noncritically Ill Adults

SALT-ED Trial
NEJM, Mar 1, 2018



13,347 ED patients who received at least 500 ml of IV isotonic crystalloid & admitted to non-ICU setting

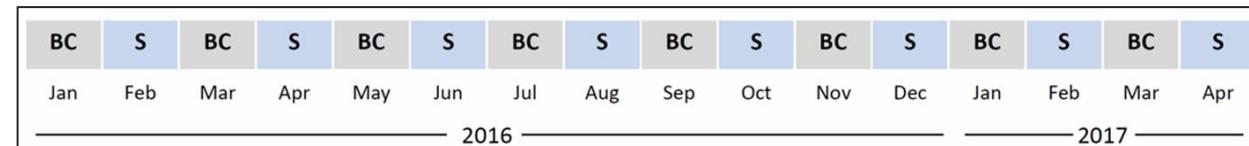


January 2016 to April 2017

Balanced Crystalloid

lactated Ringer's solution or Plasma-Lyte A

- Conducted in Vanderbilt University Medical Center Adult Emergency Department
- Single-center, pragmatic, unblinded, multiple-crossover trial
- The trial protocol guided the type of isotonic crystalloid that was administered in the ED
- Decisions regarding frequency, rate, total volume, and additive content of the crystalloids were made by the treating clinician



Balanced Crystalloids versus Saline in Noncritically Ill Adults

SALT-ED Trial
NEJM, Mar 1, 2018



Table 1. Baseline Characteristics of the Patients.*

Characteristic	Balanced Crystalloids (N=6708)	Saline (N=6639)
Median age (IQR) — yr	54 (37–67)	53 (37–67)
Female sex — no. (%)	3507 (52.3)	3379 (50.9)
Race — no. (%)†		
White	5159 (76.9)	5189 (78.2)
Black	1335 (19.9)	1251 (18.8)
Other	214 (3.2)	199 (3.0)
Median Elixhauser Comorbidity Index score (IQR)‡	7 (3–14)	7 (3–14)
Admission service — no. (%)		
Medicine services		
General medicine	4747 (70.8)	4687 (70.6)
Cardiology	303 (4.5)	321 (4.8)
Neurology	117 (1.7)	144 (2.2)
Surgery services		
General surgery	1278 (19.1)	1211 (18.2)
Trauma	263 (3.9)	276 (4.2)
Median baseline serum creatinine (IQR) — mg/dl	0.84 (0.71–0.95)	0.85 (0.71–0.94)
Source of baseline creatinine — no. (%)		
Measured value in medical record	4405 (65.7)	4276 (64.4)
Calculated value by equation	2303 (34.3)	2363 (35.6)
Initial kidney function in ED		
Serum creatinine		
Mean — mg/dl	1.32±1.42	1.31±1.36
Median (IQR) — mg/dl	0.93 (0.77–1.33)	0.93 (0.77–1.32)
≥1.5 mg/dl — no. (%)	1246 (18.6)	1240 (18.7)
End-stage renal disease with long-term renal-replacement therapy — no. (%)	126 (1.9)	109 (1.6)
Stage 2 or higher acute kidney injury — no./total no. (%)§	643/6582 (9.8)	631/6530 (9.7)
Initial serum electrolytes in ED		
Sodium — mmol/liter	137.2±4.2	137.4±4.3
Chloride — mmol/liter	102.8±5.4	103.1±5.6
Potassium — mmol/liter	4.1±0.7	4.1±0.7
Bicarbonate — mmol/liter	22.7±3.8	22.8±3.7
Blood urea nitrogen — mg/dl	20±16	20±16

Table 2. 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)

BASELINE CHARACTERISTICS

- Patients in 2 groups were similar at baseline
- Most balanced crystalloids were administered as LRS (95.3%)
- Median volume for balanced crystalloid group was 1,089 ml and 1,071 ml for saline group

Balanced Crystalloids versus Saline in Noncritically Ill Adults

SALT-ED Trial
NEJM, Mar 1, 2018



Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

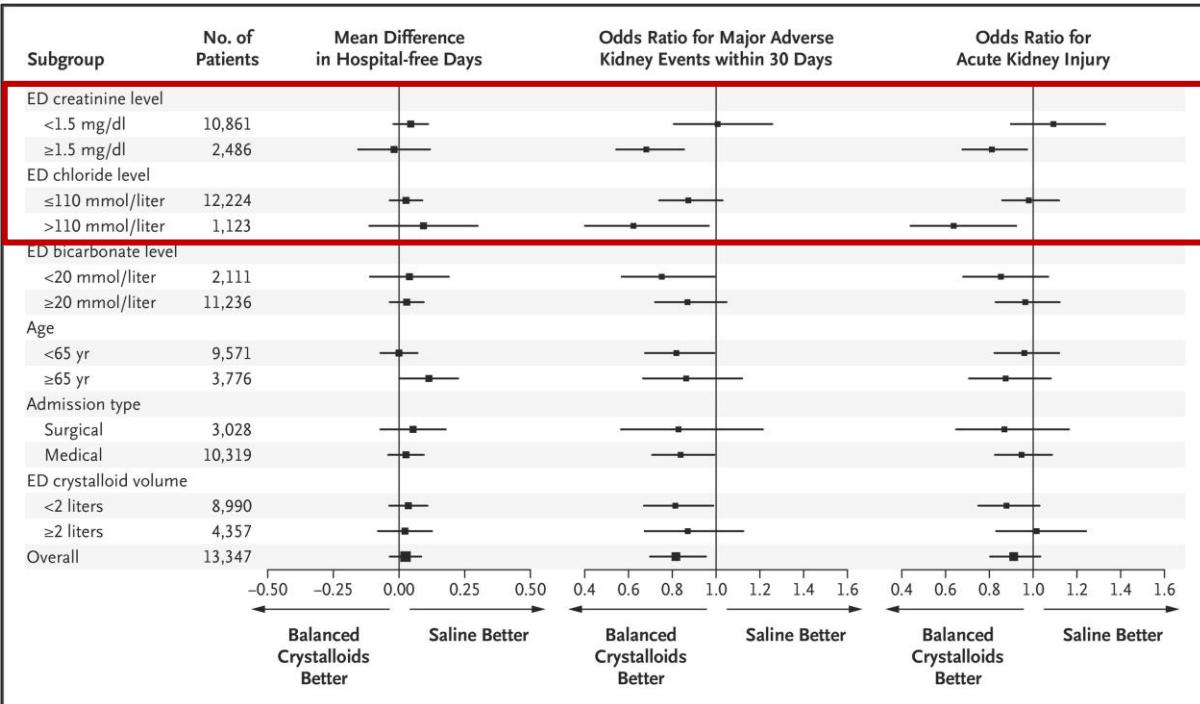
Outcome	Balanced Crystalloids (N = 6708)	Saline (N = 6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	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

OUTCOME

- No difference in the number of hospital free days at day 28 : median 25 days in each group (p=0.41)
- **Balanced-crystalloids group had a lower incidence of major adverse kidney events within 30 days** : 4.7% vs 5.6%, OR 0.82 (0.70-0.95) (p=0.01)
- The per-protocol analysis (11,780 patients) also produced similar results

Balanced Crystalloids versus Saline in Noncritically Ill Adults

SALT-ED Trial
NEJM, Mar 1, 2018

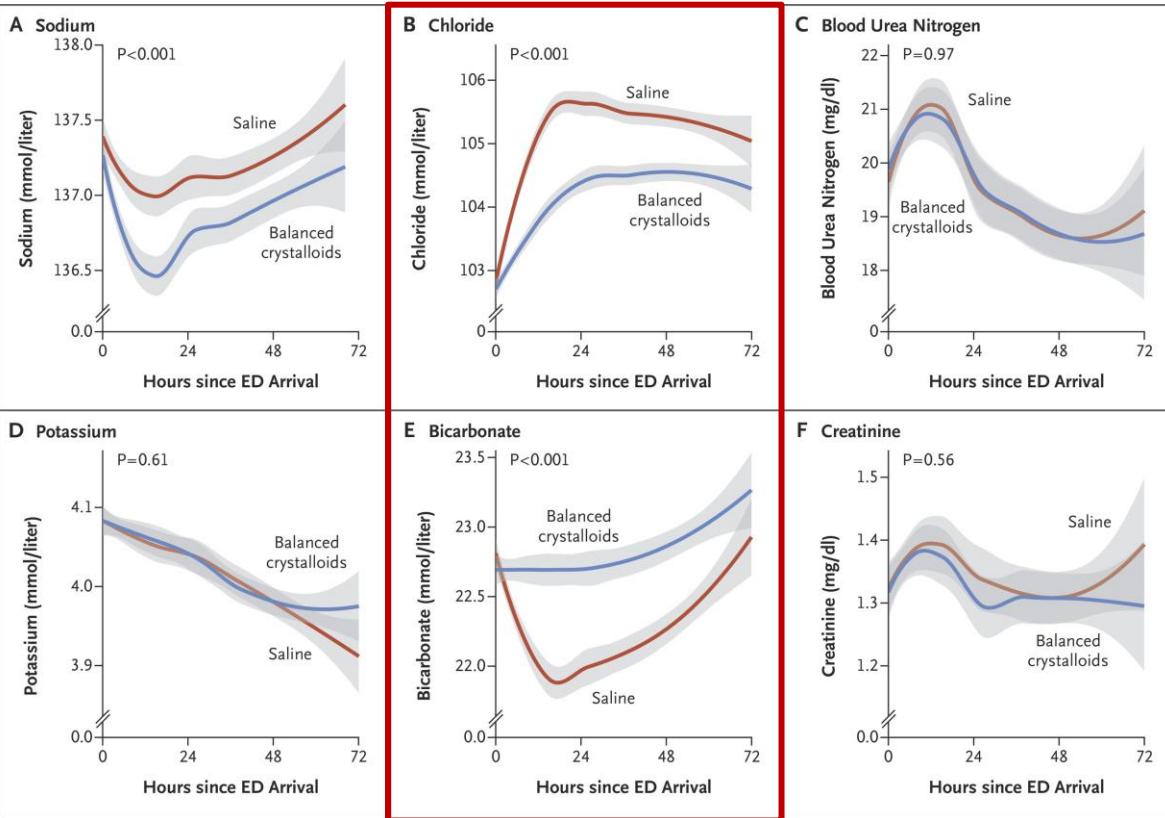


SUBGROUP ANALYSIS

- Patients who presented to the ED with renal dysfunction (serum creatinine ≥ 1.5 mg/dL) or hyperchloremia (serum chloride > 110 mmol/L) appeared to have the largest benefit from balanced crystalloids for avoiding MAKE30 and AKI

Balanced Crystalloids versus Saline in Noncritically Ill Adults

SALT-ED Trial
NEJM, Mar 1, 2018



OUTCOME: Electrolyte

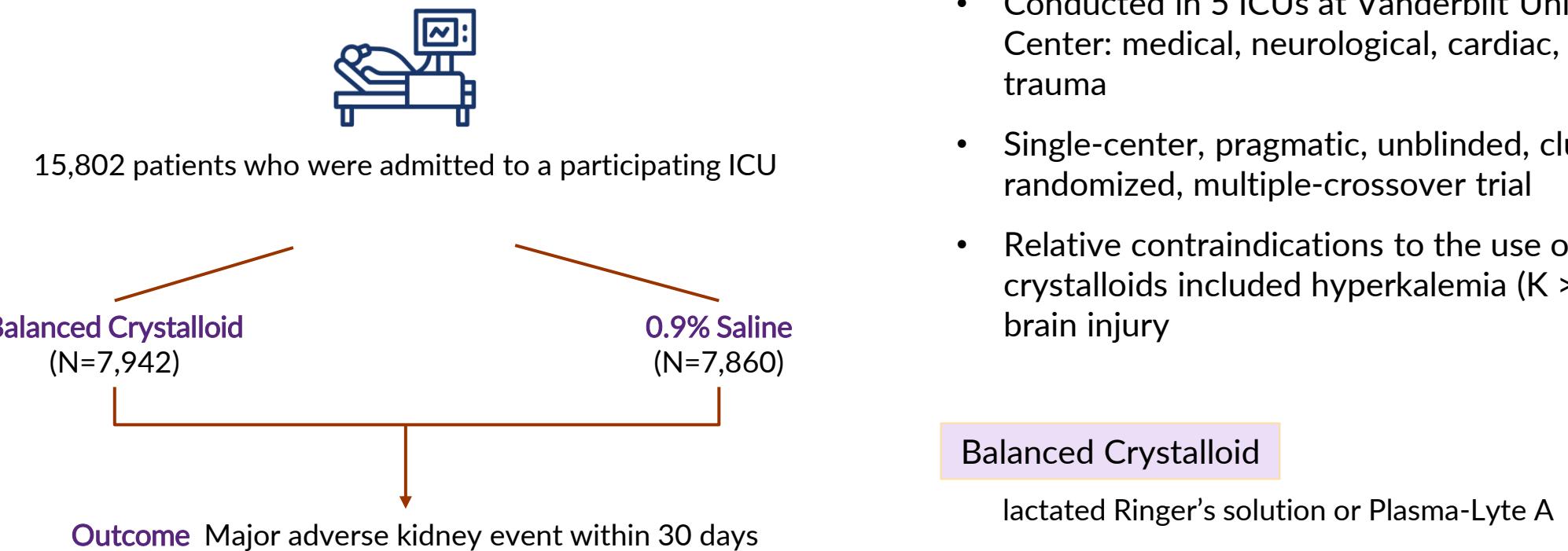
- Balanced crystalloids group had lower incidence of hyperchloremia (serum chloride >110 mmol/L) and acidemia (serum bicarbonate <20 mmol/L)

Among *noncritically ill* adults treated with intravenous fluids in the ED, there was *no difference* in hospital-free days between treatment with balanced crystalloids and treatment with saline

4 SMART Trial

Balanced Crystalloids versus Saline in Critically Ill Adults

SMART Trial
NEJM, Mar 1, 2018



- Conducted in 5 ICUs at Vanderbilt University Medical Center: medical, neurological, cardiac, surgical and trauma
- Single-center, pragmatic, unblinded, cluster randomized, multiple-crossover trial
- Relative contraindications to the use of balanced crystalloids included hyperkalemia ($K > 5.0 \text{ mmol/L}$) and brain injury

Balanced Crystalloid

lactated Ringer's solution or Plasma-Lyte A

Balanced Crystalloids versus Saline in Critically Ill Adults

SMART Trial
NEJM, Mar 1, 2018



Table 1. Participant Characteristics at Baseline.*

Characteristic	Balanced Crystalloids (N=7942)	Saline (N=7860)
Age — yr		
Median	58	58
Interquartile range	44–69	44–69
Male sex — no. (%)	4540 (57.2)	4557 (58.0)
White race — no. (%)†	6384 (80.4)	6322 (80.4)
Weight — kg‡		
Median	80	79
Interquartile range	69–96	68–95
Coexisting renal conditions — no. (%)		
Chronic kidney disease of stage 3 or higher§	1388 (17.5)	1360 (17.3)
Previous receipt of renal-replacement therapy — no. (%)	384 (4.8)	402 (5.1)
Source of admission to ICU — no. (%)		
Emergency department	3975 (50.1)	3997 (50.9)
Operating room	1732 (21.8)	1649 (21.0)
Transfer from another hospital	1038 (13.1)	1018 (13.0)
Hospital ward	788 (9.9)	780 (9.9)
Outpatient	363 (4.6)	359 (4.6)
Another ICU within hospital	46 (0.6)	57 (0.7)
Diagnosis on ICU admission — no. (%)		
Sepsis or septic shock	1167 (14.7)	1169 (14.9)
Traumatic brain injury	698 (8.8)	665 (8.5)
Mechanical ventilation — no. (%)	2723 (34.3)	2731 (34.7)
Vasopressors — no. (%)	2094 (26.4)	2058 (26.2)
Mean predicted risk of in-hospital death — % (95% CI)¶	9.4 (9.0–9.9)	9.6 (9.2–10.0)
Baseline creatinine level — mg/dl		
Median	0.89	0.89
Interquartile range	0.74–1.10	0.74–1.10
Acute kidney injury of stage 2 or higher — no. (%)**	681 (8.6)	643 (8.2)

BASELINE CHARACTERISTICS

- Patients in 2 groups were similar at baseline
- Sepsis or septic shock ~15%, TBI ~8%
- 50% of patients were admitted from ED

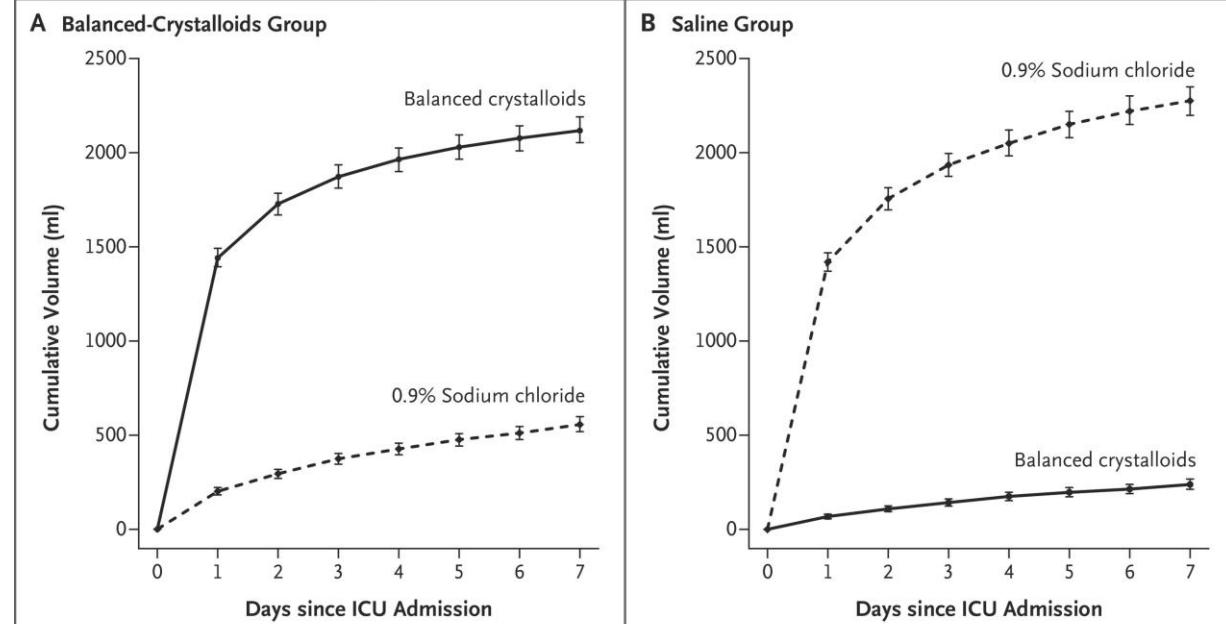
Balanced Crystalloids versus Saline in Critically Ill Adults

SMART Trial
NEJM, Mar 1, 2018



Table S4. Intravenous isotonic crystalloid in the 24 hours prior to ICU admission.

	Balanced Crystalloid (n = 7942)	Saline (n = 7860)	P value
Overall			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 125 ± 465	0 [0 – 250]; 400 ± 896	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 1200]; 790 ± 1329	0 [0 – 400]; 476 ± 1073	<0.001
Medical ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 212 ± 629	0 [0 – 1000]; 700 ± 1158	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	[0 – 1000]; 676 ± 1250	0 [0 – 0]; 178 ± 632	<0.001
Trauma ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 14 ± 159	0 [0 – 0]; 167 ± 420	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 400]; 381 ± 863	0 [0 – 0]; 184 ± 691	<0.001
Cardiac ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 60 ± 296	0 [0 – 0]; 40 ± 198	0.49
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 1500]; 761 ± 1069	456 [0 – 1450]; 807 ± 1038	0.02
Neurological ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 144 ± 427	0 [0 – 500]; 488 ± 1009	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 1600]; 899 ± 1384	0 [0 – 600]; 463 ± 954	<0.001
Surgical ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 149 ± 492	0 [0 – 500]; 428 ± 849	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	1900 [0 – 3200]; 2125 ± 2006	1200 [0 – 2900]; 1724 ± 2074	<0.001



FLUID THERAPY

- The majority of pre-ICU fluid that patients received was consistent with trial-group assignment
- Median volume** of balanced crystalloids administered to patients in the balanced-crystalloids group between ICU admission and hospital discharge or 30 days was 1,000 ml (IQR 0 to 3,210)
- Median volume** of 0.9% sodium chloride administered to patients in the saline group was 1020 ml (IQR 0 to 3,500)

Balanced Crystalloids versus Saline in Critically Ill Adults

SMART Trial
NEJM, Mar 1, 2018



Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level \geq 200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		
Secondary outcomes				
In-hospital death — no. (%)				
Before ICU discharge	528 (6.6)	572 (7.3)	0.89 (0.78 to 1.02)	0.08
Before 60 days	928 (11.7)	975 (12.4)	0.92 (0.83 to 1.02)	0.13
ICU-free days¶				0.94
Median	25.3	25.3	1.00 (0.89 to 1.13)	
Interquartile range	22.1 to 26.6	22.2 to 26.6		
Mean	21.8 \pm 8.3	21.7 \pm 8.6		
Ventilator-free days¶			1.06 (0.97 to 1.16)	0.22
Median	28.0	28.0		
Interquartile range	26.0 to 28.0	26.0 to 28.0		
Mean	24.2 \pm 8.6	23.9 \pm 8.9		
Vasopressor-free days¶			1.05 (0.97 to 1.14)	0.26
Median	28.0	28.0		
Interquartile range	27.0 to 28.0	27.0 to 28.0		
Mean	24.7 \pm 8.5	24.4 \pm 8.8		
Renal-replacement therapy-free days¶			1.11 (1.02 to 1.20)	0.01
Median	28.0	28.0		
Interquartile range	28.0 to 28.0	28.0 to 28.0		
Mean	25.0 \pm 8.6	24.8 \pm 8.9		

Table 2. Clinical Outcomes.*

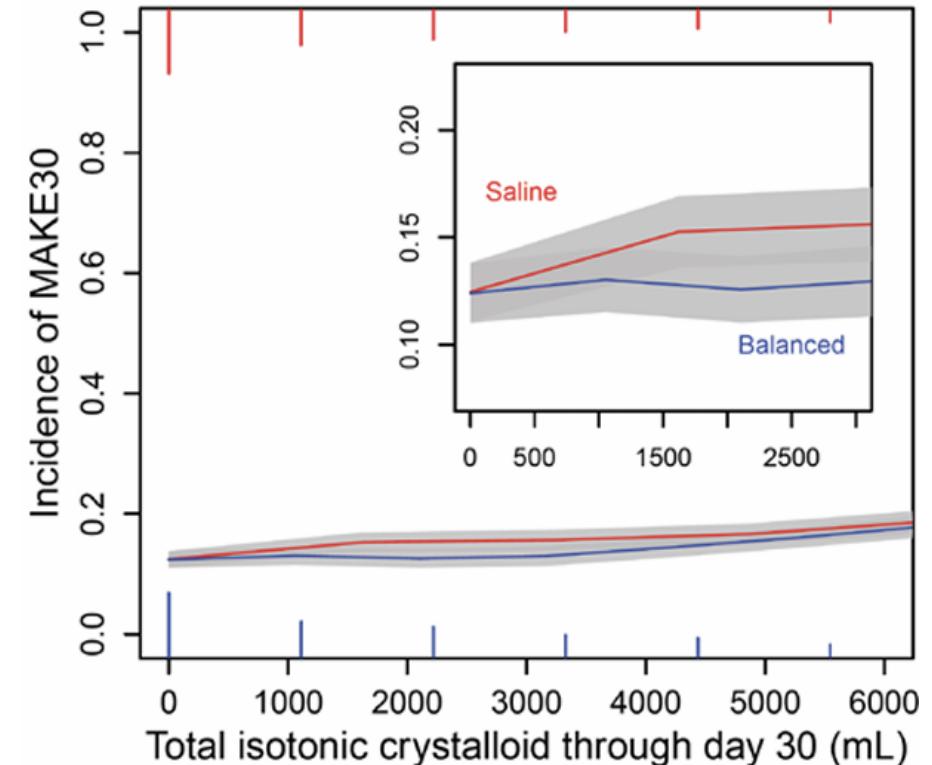
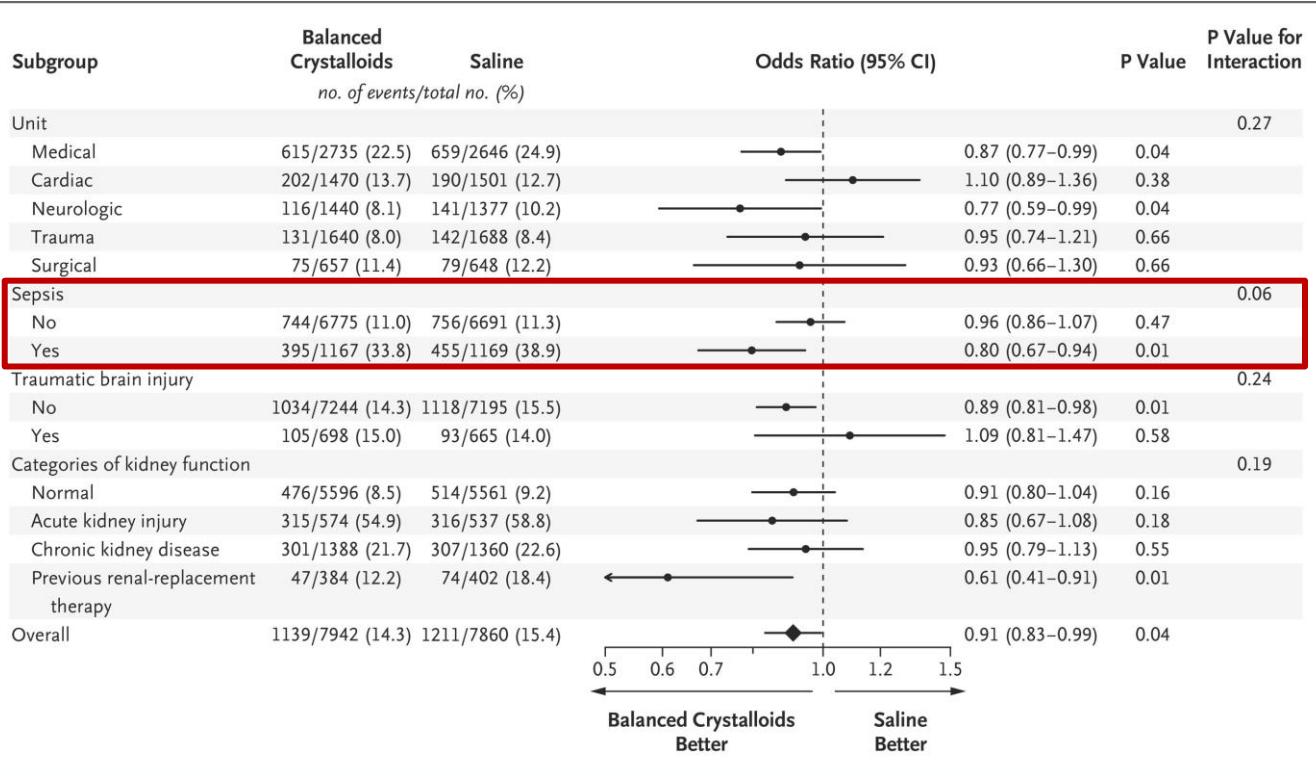
Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Secondary renal outcomes§				
Stage 2 or higher AKI developing after enrollment — no./total no. (%)	807/7558 (10.7)	858/7458 (11.5)	0.91 (0.82 to 1.01)	0.09
Creatinine — mg/dl***				
Highest before discharge or day 30			1.01 (0.97 to 1.05)	0.58
Median	0.99	0.99		
Interquartile range	0.78 to 1.53	0.78 to 1.52		
Change from baseline to highest value			0.98 (0.94 to 1.02)	0.35
Median	0.04	0.04		
Interquartile range	-0.08 to 0.31	-0.08 to 0.32		
Final value before discharge or 30 days			1.02 (0.97 to 1.06)	0.51
Median	0.83	0.83		
Interquartile range	0.70 to 1.11	0.70 to 1.11		

OUTCOME

- MAKE 30 was significantly greater in saline group : 14.3% vs 15.4% (p=0.04)

Balanced Crystalloids versus Saline in Critically Ill Adults

SMART Trial
NEJM, Mar 1, 2018

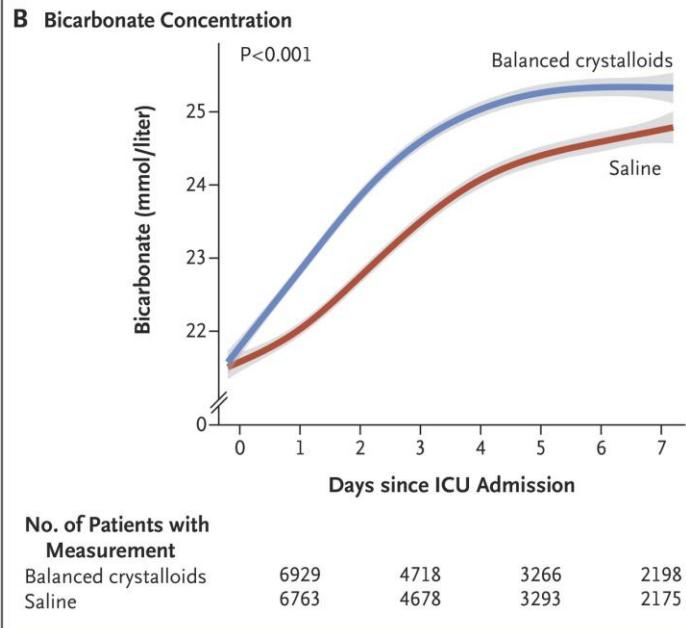
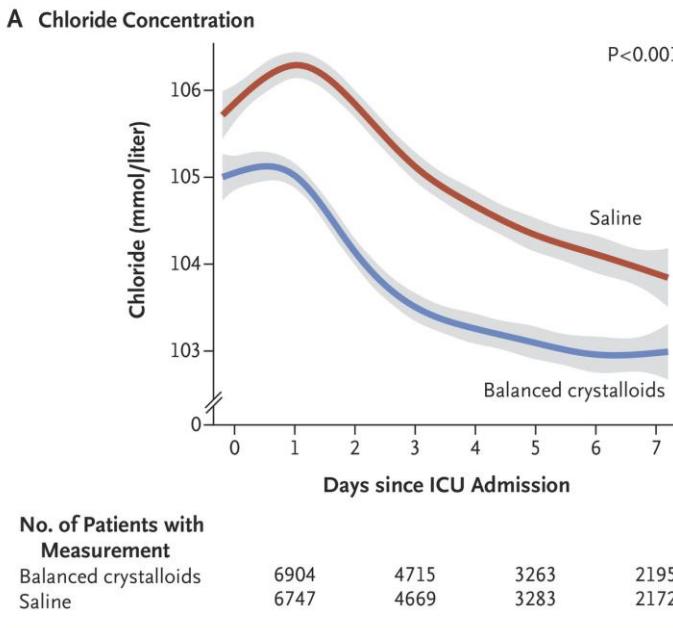


SUBGROUP ANALYSIS

- The difference in the rate of MAKE30 was greater among patients who received larger volumes of isotonic crystalloid and among patients with sepsis

Balanced Crystalloids versus Saline in Critically Ill Adults

SMART Trial
NEJM, Mar 1, 2018



OUTCOME: Electrolyte

- Balanced crystalloids group had lower incidence of hyperchloremia (24.5% vs. 35.6%, P<0.001) and acidemia (35.2% vs. 42.1%, P<0.001)
- Differences between groups in chloride and bicarbonate concentration were greater for patients who received larger volumes of isotonic crystalloid

Among *critically ill* adults, the use of *balanced crystalloids* for intravenous fluid administration resulted in a *lower rate of MAKE30* than the use of saline

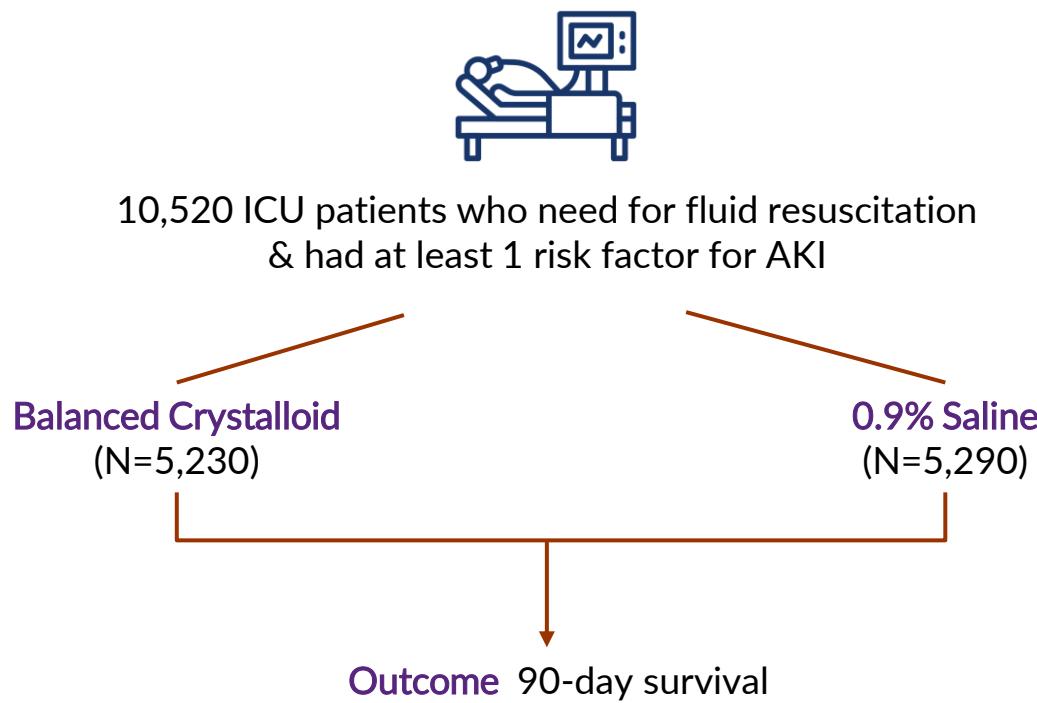
5

BaSICS Trial

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

The BaSICS Randomized Clinical Trial

BaSICS Trial
JAMA, Aug 10, 2021



- Double-blind, factorial, randomized clinical trial
- 75 ICUs in Brazil
- 2 different fluid types: balanced solution vs saline solution
- 2 different infusion rates: 333 ml/h vs 999 ml/h (reported separately)

Balanced Crystalloid

Plasma-Lyte 148

Risk Factors for AKI

- Age >65 yr
- Hypotension (MAP <65 mmHg, SBP <90 mmHg, or vasopressor used)
- Sepsis
- Required MV or NIV ≥12 h
- Oliguria or Cr >1.2 in women and >1.4 in men
- Liver cirrhosis or acute liver failure

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

The BaSICS Randomized Clinical Trial

BaSICS Trial
JAMA, Aug 10, 2021



Table 1. Baseline Characteristics of Patients in the Intensive Care Unit (ICU)

Characteristic	Balanced solution, No./total (%) ^a	Saline solution, No./total (%) ^{a,b}
No. of patients	5230	5290
Age, mean (SD), y	60.9 (17.0)	61.2 (16.9)
Sex, No. (%)		
Female	2321 (44.4)	2334 (44.1)
Male	2909 (55.6)	2956 (55.9)
Admission type		
No. of missing patients	18	9
Planned (elective surgery)	2491/5212 (47.8)	2588/5281 (49.0)
Unplanned ^c	2721/5212 (52.2)	2693/5281 (51.0)
Emergency department	1194/5212 (22.9)	1188/5281 (22.5)
Nonelective surgery	653/5212 (12.5)	652/5281 (12.3)
Ward	549/5212 (10.5)	507/5281 (9.6)
Transfer from another hospital	288/5212 (5.5)	306/5281 (5.8)
Transfer from another ICU	37/5212 (0.7)	40/5281 (0.8)
Illness severity at enrollment		
APACHE II score ^d		
No. of patients	5195	5271
No. of missing patients	35	29
Median (IQR)	12 (8-17)	12 (8-17)
SOFA score ^e		
No. of patients	5195	5271
No. of missing patients	35	29
Median (IQR)	4 (2-7)	4 (2-7)
KDIGO stage ^f	1683/5198 (32.4)	1765/5265 (33.5)
No. of missing patients	32	25
Sepsis	966/5212 (18.5)	1015/5280 (19.2)
No. of missing patients	18	10
Traumatic brain injury	247/5212 (4.7)	236/5281 (4.5)
No. of missing patients	18	9
Hypotension ^g	3161/5211 (60.7)	3195/5280 (60.5)
No. of missing patients	19	10
Type of mechanical ventilation		
No. of missing patients	18	9
Noninvasive for >12 h	332/5212 (6.4)	341/5281 (6.5)
Invasive	2304/5212 (44.2)	2340/5281 (44.3)
Serum creatinine level, mean (SD), mg/dL		
No. of patients	5187	5247
No. of missing patients	43	43
Mean (SD)	1.2 (0.9)	1.2 (0.9)

Table 1. Baseline Characteristics of Patients in the Intensive Care Unit (ICU)

Characteristic	Balanced solution, No./total (%) ^a	Saline solution, No./total (%) ^{a,b}
Creatinine level, mg/dL		
<1.5	4139/5187 (79.8)	4162/5247 (79.3)
1.6-2.5	719/5187 (13.9)	720/5247 (13.7)
>2.5	329/5187 (6.3)	365/5247 (7.0)
Cirrhosis or acute liver failure	132/5212 (2.5)	135/5281 (2.5)
No. of missing patients	18	9
Heart failure	593/5212 (11.4)	543/5281 (10.3)
No. of missing patients	18	9
Time from ICU admission to randomization, d		
No. of patients	5212	5281
No. of missing patients	18	9
Median (2.5%-97.5%)	0 (0-1)	0 (0-1)
Administration of balanced solution within the 24 h before enrollment ^h		
No. of missing patients	18	10
Received any	2503/5212 (48.0)	2561/5280 (48.5)
Received >1000 mL	1626/5212 (31.2)	1692/5280 (32.0)
Volume of balanced solutions administered within the 24 h before enrollment		
No. of patients	5212	5280
No. of missing patients	18	10
Median (IQR), mL	0 (0-1500)	0 (0-1500)
Administration of saline solution within the 24 h before enrollment		
No. of missing patients	18	10
Received any	1987/5212 (38.1)	1971/5280 (37.3)
Received >1000 mL	935/5212 (17.9)	994/5280 (18.8)
Volume of saline solution administered within the 24 h before enrollment		
No. of patients	5212	5280
No. of missing patients	18	10
Median (IQR), mL	0 (0-1000)	0 (0-1000)
Administration of any fluid within the 24 h before enrollment		
No. of missing patients	18	10
Received any	3551/5212 (68.1)	3609/5280 (68.4)
Received >1000 mL	2327/5212 (44.6)	2427/5280 (46)
Volume of any fluids administered within the 24 h before enrollment		
No. of patients	5212	5280
No. of missing patients	18	10
Median (IQR), mL	1000 (0-2500)	1000 (0-2500)

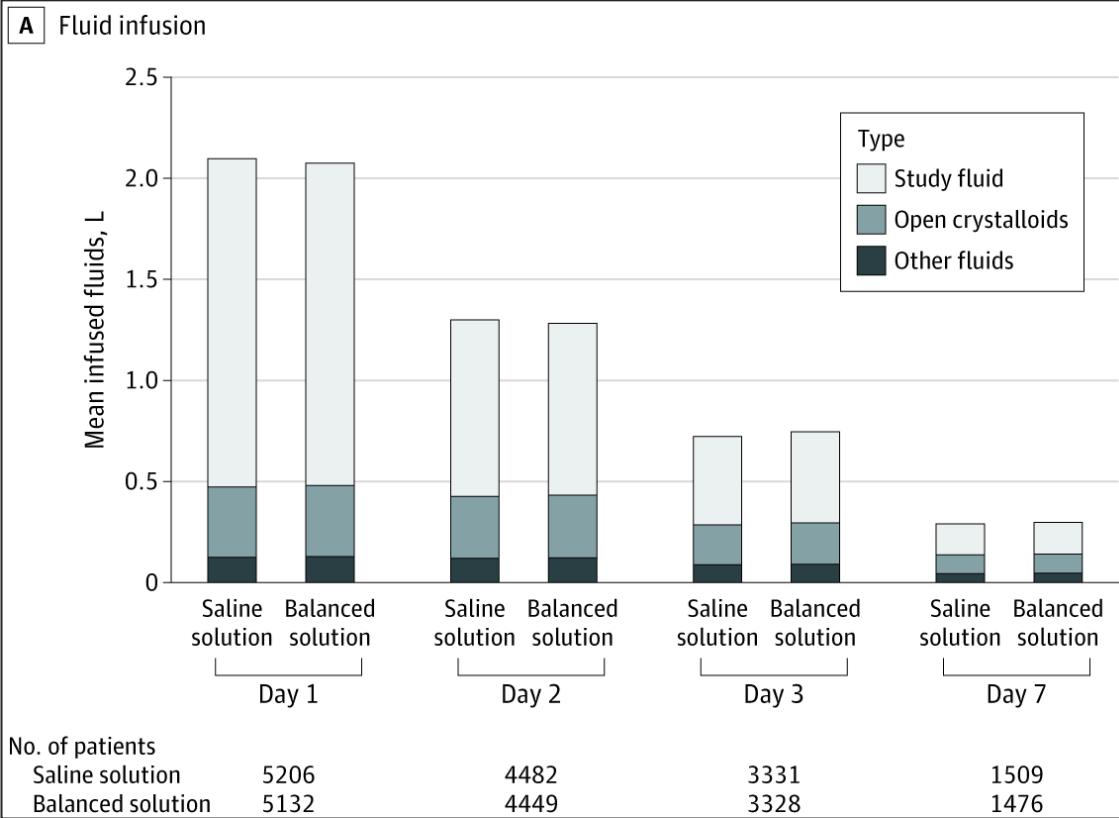
BASELINE CHARACTERISTICS

- Patients in 2 groups were similar at baseline
- Elective surgery 48.4%
- 68% received crystalloid fluid bolus before ICU
 - 45% received >1 L

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

The BaSICS Randomized Clinical Trial

BaSICS Trial
JAMA, Aug 10, 2021



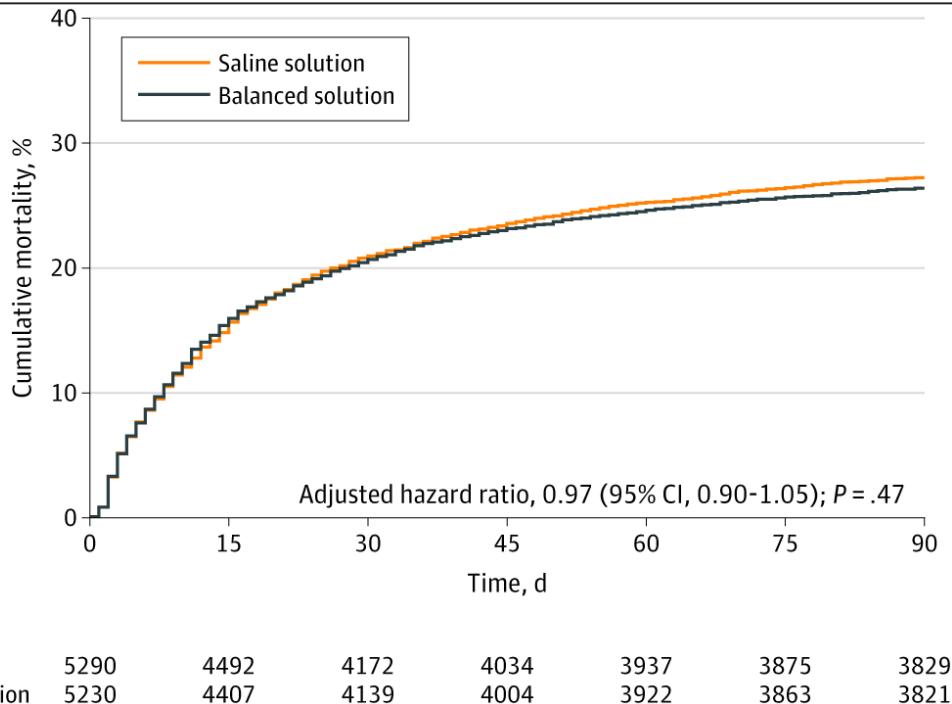
FLUID THERAPY

- Both groups received a median of 1.5 L of fluid during the first day after enrollment
- During the first 3 days
 - Median accumulated fluid = 4.1 L
 - Median accumulated study fluid = 2.9 L

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

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OUTCOME

- No significant difference in 90-day mortality between 2 groups : 26.4% vs 27.2% (HR 0.97, p=0.47)

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

The BaSICS Randomized Clinical Trial

BaSICS Trial
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Table 2. Primary, Secondary, and Tertiary Outcomes Comparing a Balanced Solution With Saline Solution (0.9% Sodium Chloride)

Outcomes	No./total (%)		Absolute difference (95% CI)	Effect measure (95% CI)
	Balanced solution	Saline solution		
Secondary outcomes				
Incidence of acute kidney failure with need for kidney replacement therapy within 90 d per 1000 patient-days	414/471 (0.88)	445/476 (0.93)	-0.05 (-0.15 to 0.06)	RR, 0.95 (0.83 to 1.08)
At day 1	28/5218 (0.5)	30/5287 (0.6)		
At day 2	115/5174 (2.2)	137/5242 (2.6)		
At day 3	181/5052 (3.6)	213/5123 (4.2)		
At day 7	267/4808 (5.6)	314/4884 (6.4)		
In the hospital (≥ 1 episode during stay)	393/5218 (7.5)	427/5287 (8.1)	-0.5 (-1.5 to 0.4)	OR, 0.93 (0.81 to 1.06)
Acute kidney injury assessed as KDIGO stage $\geq 2^b$				
At day 3	850/3128 (27.2)	859/3094 (27.8)	-1.9 (-4.0 to 0.2)	OR, 0.99 (0.88 to 1.11)
At day 7	276/1180 (23.4)	273/1170 (23.3)	-1.5 (-3.6 to 0.6)	OR, 1.07 (0.88 to 1.30)
KDIGO stage ≥ 2 or death				
At day 3	851/3128 (27.2)	865/3094 (28.0)	-1.9 (-4.0 to 0.2)	OR, 0.98 (0.87 to 1.10)
At day 7	278/1180 (23.6)	275/1170 (23.5)	-1.5 (-3.6 to 0.6)	OR, 1.07 (0.88 to 1.30)
Total SOFA score at day 3 ^c				
No. of patients	3789	3846		
Median (IQR)	4 (2 to 6)	4 (2 to 6)	0.09 (-0.02 to 0.16)	
SOFA score >2 at day 3				
Cardiovascular ^d	1319/3789 (34.8)	1271/3846 (33.0)	1.7 (-0.4 to 3.9)	OR, 1.11 (1.00 to 1.22)
Neurological ^e	654/3789 (17.3)	636/3846 (16.5)	0.6 (-0.8 to 1.9)	OR, 1.06 (0.93 to 1.22)
Coagulation ^f	163/3789 (4.3)	163/3846 (4.2)	0 (-0.8 to 0.9)	OR, 1.02 (0.82 to 1.27)
Respiratory ^g	266/3789 (7.0)	258/3846 (6.7)	0.2 (-0.7 to 1.1)	OR, 1.04 (0.87 to 1.24)
Hepatic ^h	44/3789 (1.2)	49/3846 (1.3)	-0.1 (-0.5 to 0.3)	OR, 0.94 (0.65 to 1.36)
Total SOFA score at day 7 ^c				
No. of patients	1531	1594		
Median (IQR)	4 (2 to 7)	4 (2 to 7)	0.27 (0.08 to 0.45)	
SOFA score >2 at day 7				
Cardiovascular ^d	420/1531 (27.4)	409/1594 (25.7)	2.0 (-1.0 to 5.1)	OR, 1.14 (0.97 to 1.34)
Neurological ^e	492/1531 (32.1)	415/1594 (26.0)	5.0 (2.3 to 7.8)	OR, 1.40 (1.18 to 1.66)
Coagulation ^f	62/1531 (4.0)	70/1594 (4.4)	-0.1 (-1.3 to 1.0)	OR, 1.01 (0.73 to 1.39)
Respiratory ^g	171/1531 (11.2)	154/1594 (9.7)	1.3 (-0.4 to 2.9)	OR, 1.21 (0.96 to 1.52)
Hepatic ^h	25/1531 (1.6)	27/1594 (1.7)	0 (-0.6 to 0.6)	OR, 1.04 (0.67 to 1.62)
Days not requiring mechanical ventilation within 28 d			0.14 (-0.35 to 0.64)	
No. of patients	5217	5287		
Median (IQR)	27 (13 to 28)	27 (10 to 28)		

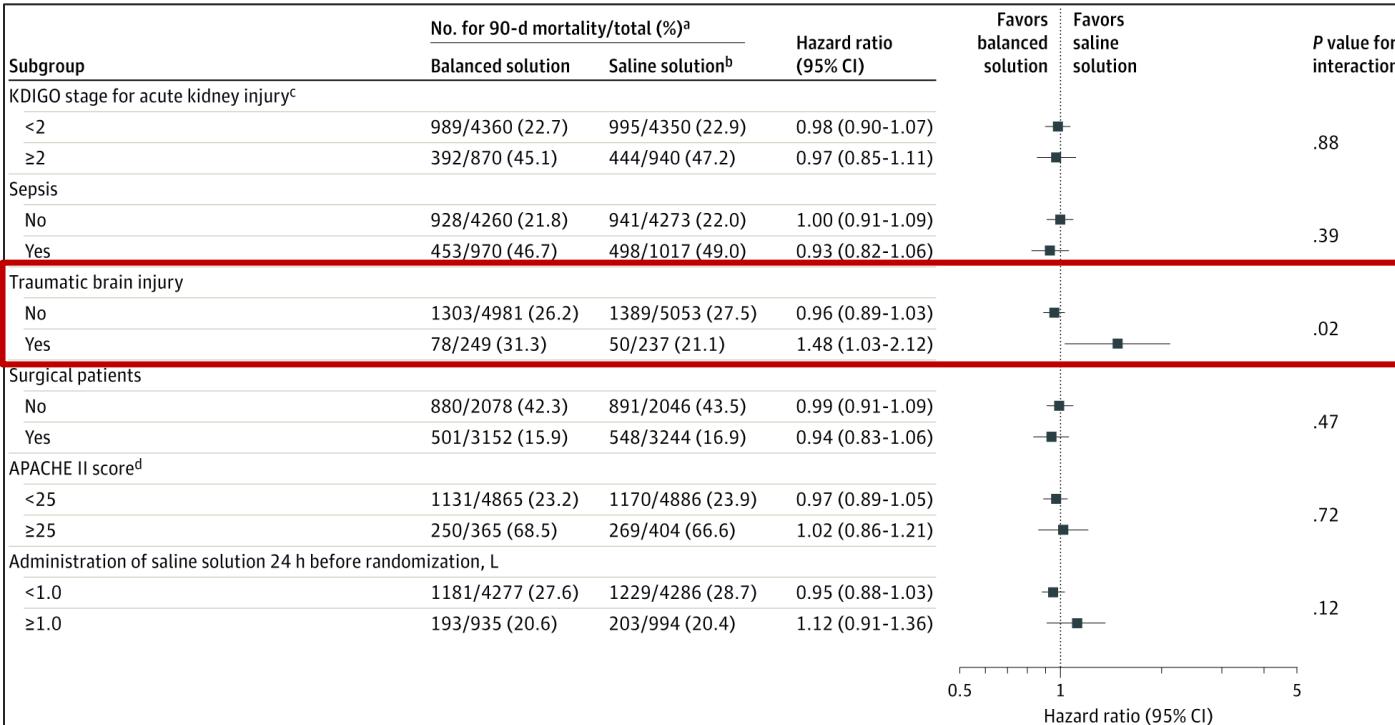
OUTCOME

- Balanced solution group had significant higher proportion of patients with high neurological SOFA score (>2) at day 7
- No significant different in rate of RRT

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

The BaSICS Randomized Clinical Trial

BaSICS Trial
JAMA, Aug 10, 2021



SUBGROUP ANALYSIS

- Significant interaction between presence of TBI, fluid type, and 90-day mortality : 31.3% vs 21.1% (HR 1.48, p=0.02)

Among critically ill patients requiring fluid challenges, use of a balanced solution compared with 0.9% saline solution *did not* significantly reduce 90-day mortality

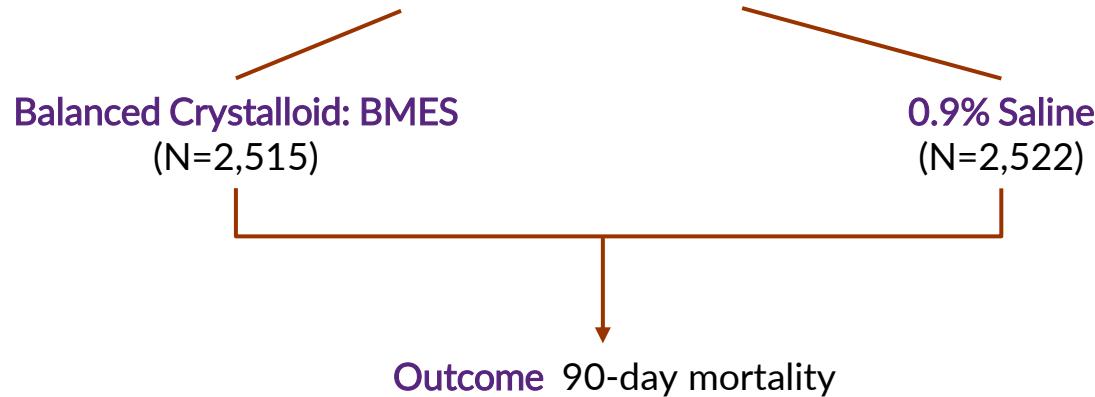
6 PLUS Study

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

PLUS Study
NEJM, Mar 3, 2022



5,037 ICU patients who need for fluid resuscitation



- Investigator-initiated, double-blind, parallel-group, randomized, controlled trial
- 53 ICUs in Australia (41) and New Zealand (12)
- The treating clinicians decided the amount and rate of fluid administration

Balanced Crystalloid

Plasma-Lyte 148

September 2017 to December 2020

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

PLUS Study
NEJM, Mar 3, 2022



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	BMES Group (N=2515)	Saline Group (N=2522)
Age — yr	61.7±16.4	62.1±16.5
Female sex — no./total no. (%)	937/2515 (37.3)	1011/2522 (40.1)
ICU admission source — no./total no. (%)		
Emergency department	834/2451 (34.0)	779/2448 (31.8)
Hospital floor, other hospital, or other ICU	524/2451 (21.4)	546/2448 (22.3)
Admitted after emergency surgery	657/2451 (26.8)	657/2448 (26.8)
Admitted after elective surgery	436/2451 (17.8)	466/2448 (19.0)
Median APACHE II score (IQR)†	19.0 (14.0–26.0)	19.0 (14.0–25.0)
Mechanical ventilation type — no./total no. (%)		
Invasive	1861/2451 (75.9)	1881/2448 (76.8)
Noninvasive	70/2451 (2.9)	58/2448 (2.4)
Receipt of new renal-replacement therapy — no./total no. (%)	47/2451 (1.9)	54/2448 (2.2)
Median time from ICU admission to randomization (IQR) — hr‡	2.0 (1.0–7.0)	2.0 (0.0–7.0)
Sepsis according to SIRS criteria — no./total no. (%)§	1048/2451 (42.8)	1023/2448 (41.8)
Sepsis according to Sepsis-3 criteria — no./total no. (%)§	1074/2450 (43.8)	1043/2447 (42.6)
Hospital admission for trauma — no./total no. (%)	201/2451 (8.2)	214/2448 (8.7)
Median SOFA score according to domain (IQR)¶		
Respiratory domain	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Cardiovascular domain	3.0 (1.0–4.0)	3.0 (1.0–4.0)
Clinical measure		
Creatinine level — mg/dl	1.44±1.24	1.42±1.27
Heart rate — beats/min	92.1±23.4	92.9±23.4
Mean arterial pressure — mm Hg	73.2±12.8	73.8±13.0
Arterial blood pH	7.3±0.1	7.3±0.1
Base excess — mmol/liter	-4.2±5.6	-4.1±5.4
Serum lactate level — mmol/liter	2.7±2.5	2.7±2.4
Chloride level — mmol/liter	105.4±6.0	105.6±5.8

Table S3. Fluids received in the 24 hours prior to randomisation

	Balanced (N = 2451)	0.9% Saline (N = 2447)	Total (N = 4898)
0.9% Saline (mls)			
Mean (SD)	1060.5 (1280.83)	1006.7 (1211.31)	1033.7 (1246.75)
Median (Q1; Q3)	625.0 (28.0; 1700.0)	516.0 (17.0; 1606.0)	571.0 (20.0; 1631.0)
min max	0 11000	0 7500	0 11000
Balanced multi-electrolyte solution (mls)			
Mean (SD)	606.1 (1505.64)	655.9 (1590.54)	631.0 (1548.68)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 80.0)	0.0 (0.0; 40.0)
min max	0 11000	0 13000	0 13000
>=500 mL of “other group” fluid prior to randomisation			
	1360/2451 (55.5%)	567/2447 (23.2%)	1927/4898 (39.3%)

BASELINE CHARACTERISTICS

- The baseline characteristics of the patients were similar in both groups
- 42.3% had sepsis
- Within 24 hours before randomization, the patients in the two groups had received similar amounts and types of intravenous fluid

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

PLUS Study
NEJM, Mar 3, 2022

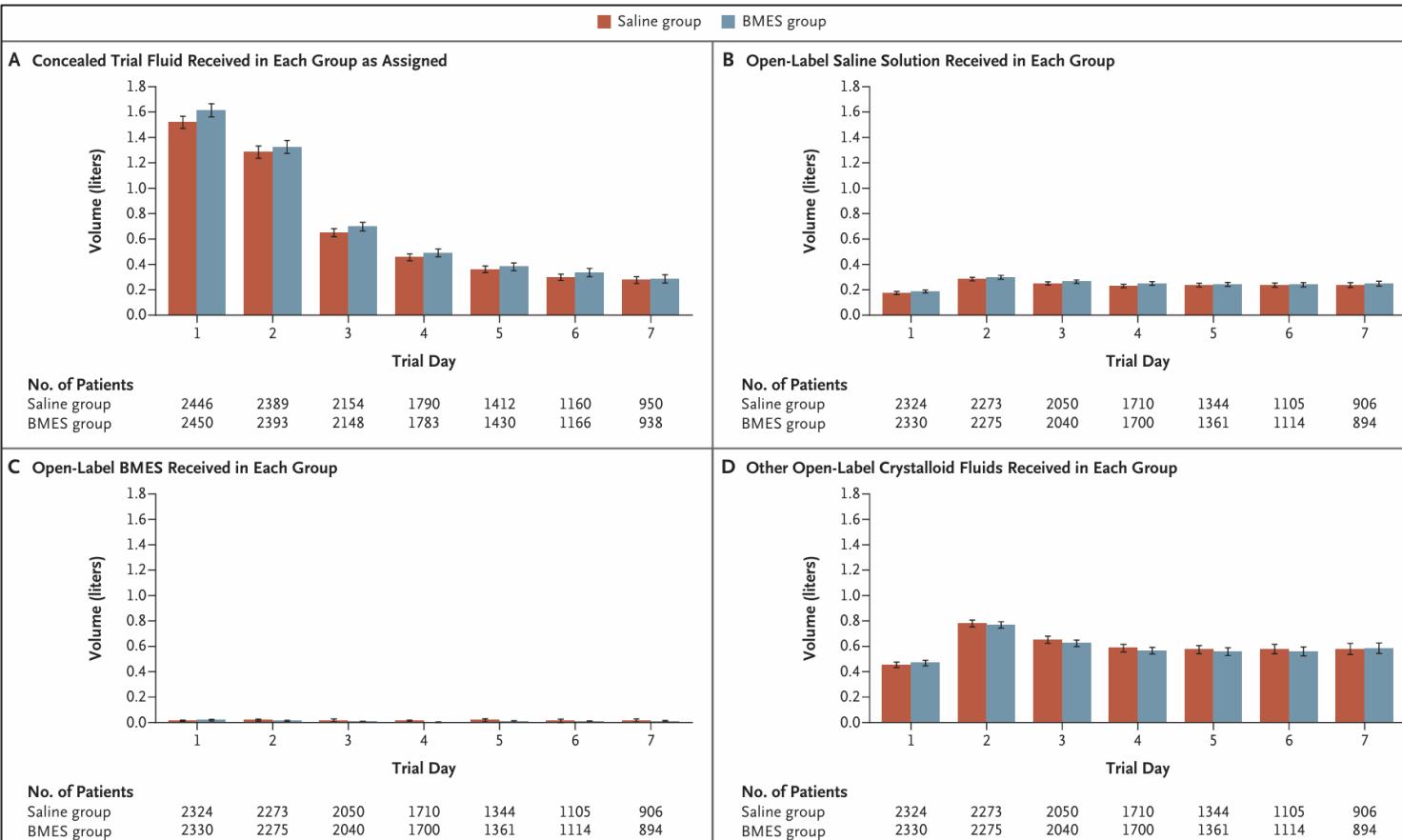


Figure 1. Volume of the Trial Fluids and Other Crystalloid Fluids Administered during the First 7 Days after Randomization.

FLUID THERAPY

- Median duration of treatment with the assigned trial fluid = 6.0 days
- Median volume of trial fluid received was 3.9 L in BMES group & 3.7 L in saline group
- 63.0% in the BMES group received ≥ 500 ml of open-label saline
- 3.5% in the saline group received ≥ 500 ml of BMES

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

PLUS Study
NEJM, Mar 3, 2022



Table 2. Trial Outcomes.*

Outcome	BMES Group (N=2515)	Saline Group (N=2522)	Odds Ratio (95% CI)	Absolute Difference (95% CI)†
Death from any cause within 90 days after randomization				
Primary analyses				
Unadjusted — no./total no. (%)	530/2433 (21.8)	530/2413 (22.0)	0.99 (0.86 to 1.14)	-0.15 (-3.60 to 3.30)‡
Adjusted§			0.99 (0.86 to 1.14)	-0.17 (-3.51 to 3.16)
Multiple imputation¶			0.99 (0.86 to 1.13)	-0.22 (-3.61 to 3.18)
Secondary analyses				
Secondary analysis 1			1.19 (0.96 to 1.46)	2.78 (-1.71 to 7.27)
Secondary analysis 2			0.94 (0.77 to 1.15)	-0.95 (-5.13 to 3.24)
Secondary analysis 3			1.06 (0.79 to 1.42)	0.91 (-4.65 to 6.47)
Inverse probability of treatment weighting — no./total no. (%)	176/858 (20.5)**	298/1574 (18.9)**	1.06 (0.88 to 1.28)	1.01 (-3.49 to 5.51)
Other mortality outcomes				
Death from any cause within 90 days after randomization while in the ICU — no./total no. (%)	395/2433 (16.2)	371/2413 (15.4)	1.07 (0.91 to 1.25)	0.89 (-2.03 to 3.81)
Death from any cause within 90 days after randomization while in the hospital — no./total no. (%)	503/2433 (20.7)	511/2413 (21.2)	0.97 (0.85 to 1.12)	-0.49 (-3.83 to 2.85)
Death from any cause within 28 days after randomization — no./total no. (%)	451/2433 (18.5)	445/2413 (18.4)	1.01 (0.87 to 1.17)	0.12 (-3.31 to 3.56)
Other binary outcomes				
Receipt of new renal-replacement therapy — no./total no. (%)	306/2403 (12.7)	310/2394 (12.9)	0.98 (0.83 to 1.16)	-0.20 (-2.96 to 2.56)
Receipt of vasoactive drugs — no./total no. (%)	2115/2453 (86.2)	2133/2448 (87.1)	0.92 (0.78 to 1.09)	-0.85 (-4.06 to 2.36)
Continuous outcomes				
Maximum creatinine level in the ICU during days 1 to 7 — mg/dl	1.76±1.44	1.75±1.43		0.01 (-0.04 to 0.06)
Maximum increase in creatinine level in the ICU — mg/dl	0.41±1.06	0.41±1.02		0.01 (-0.05 to 0.06)
Days alive and free of mechanical ventilation	68.3±33.4	68.2±33.4		0.06 (-1.79 to 1.91)
Days alive and free of vasoactive agents	69.9±32.9	69.9±32.7		0.03 (-1.80 to 1.85)
Days alive outside the ICU	65.3±32.8	65.3±32.8		0.05 (-1.77 to 1.87)
Days alive outside the hospital	52.9±31.7	52.3 ±31.5		0.62 (-1.15 to 2.38)
Adverse events				
Severe electrolyte or acid-base disturbance — no.	1	4		
Cardiac arrest possibly related to trial fluid — no.	0	1		
Drug precipitation in trial fluid — no.	2	0		

OUTCOME

- No significant different in 90-day mortality : 21.8% vs 22.0% (ARR -0.15%, p=0.90)
- No significant difference in new RRT, receipt of vasoactive drugs, days alive and free of mechanical ventilation, maximum creatinine level or increase in creatinine

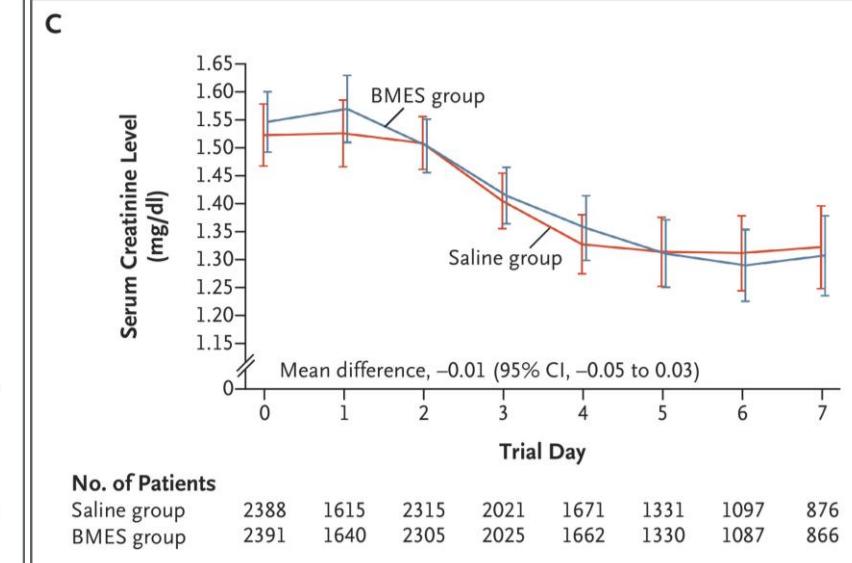
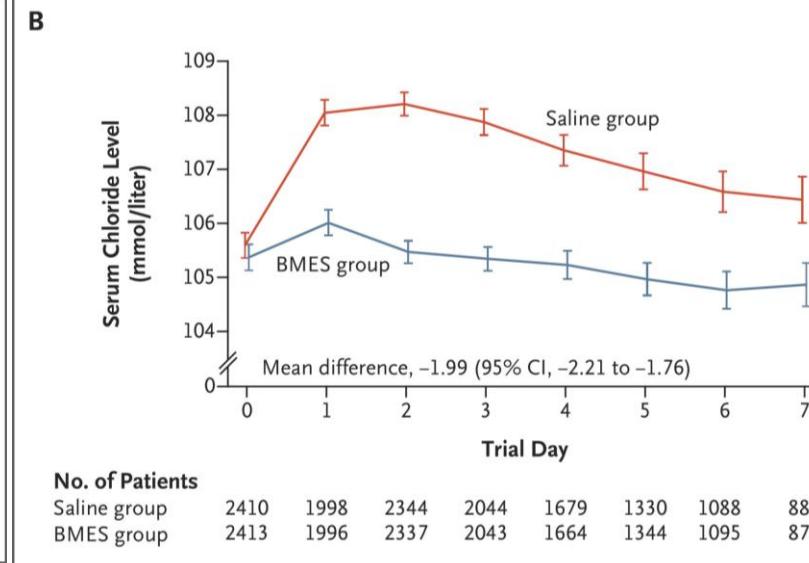
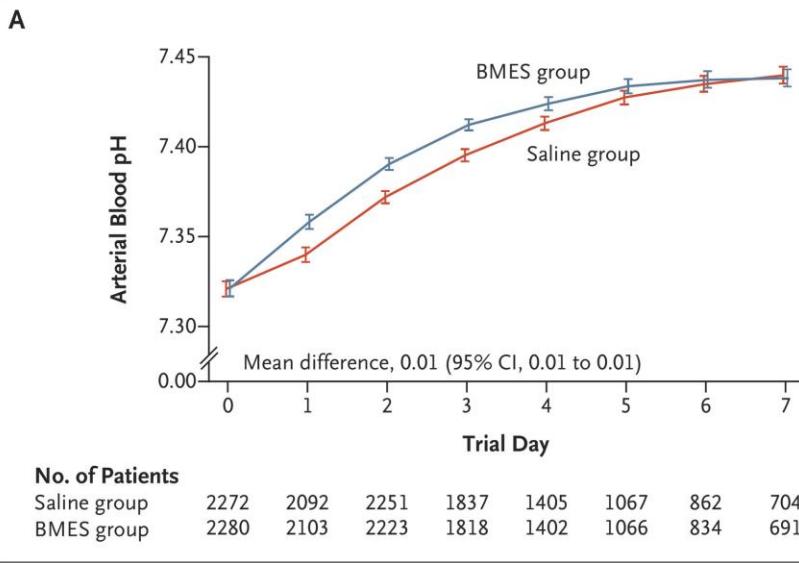
SECONDARY ANALYSIS

Excluded patients who received > 500ml of alternate fluid

- No change in primary outcome

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

PLUS Study
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OUTCOME

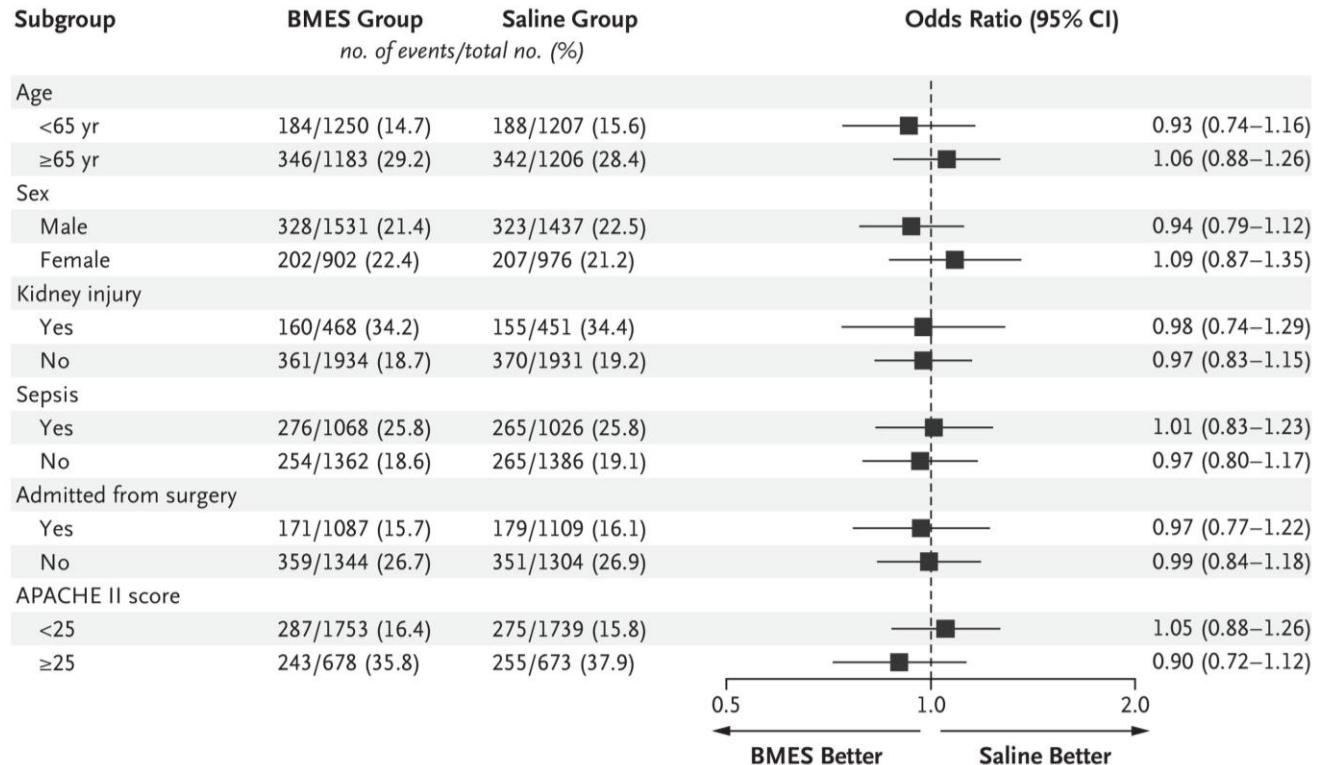
- The use of saline resulted in a significantly higher serum chloride level and a lower pH than the use of BMES but had no significant effect on kidney function

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

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B Subgroup Analysis of Death from Any Cause



SUBGROUP ANALYSIS

- No statistically significant differences noted in any of pre-specified subgroups

In heterogeneous population of critically ill adults, *no evidence* that the use of BMES in preference to saline in the ICU resulted in a lower all-cause mortality or risk of acute kidney injury

Comparison of Type of Crystalloid Studies

	SPLIT	SALT-ED	SMART	BaSICS	PLUS
Location	New Zealand	US	US	Brazil	Australia & New Zealand
Population	2278	13347	15802	10520	5037
Protocol					
Patients	ICU patients	ED & non-ICU	ICU patients	ICU patients with risk for AKI	ICU patients
Intervention	Plasma-lyte 148	LRS Plasma-lyte A	LRS Plasma-lyte A	Plasma-lyte 148	Plasma-lyte 148
Control	0.9% NaCl	0.9% NaCl	0.9% NaCl	0.9% NaCl	0.9% NaCl
Median volume	2000 ml	1080 ml	1000 ml	1500 ml in first 24 h	3900 ml in first 7 d

Comparison of Type of Crystalloid Studies

	SPLIT	SALT-ED	SMART	BaSICS	PLUS
Primary Outcome					
Primary outcome	AKI in 90 days	Hospital-free day at day 28	MAKE30	90-d mortality	90-d mortality
Intervention	9.6%	25 days	14.3%	26.4%	21.8%
Control	9.2%	25 days	15.4%	27.2%	22.0%

Comparison of Type of Crystalloid Studies

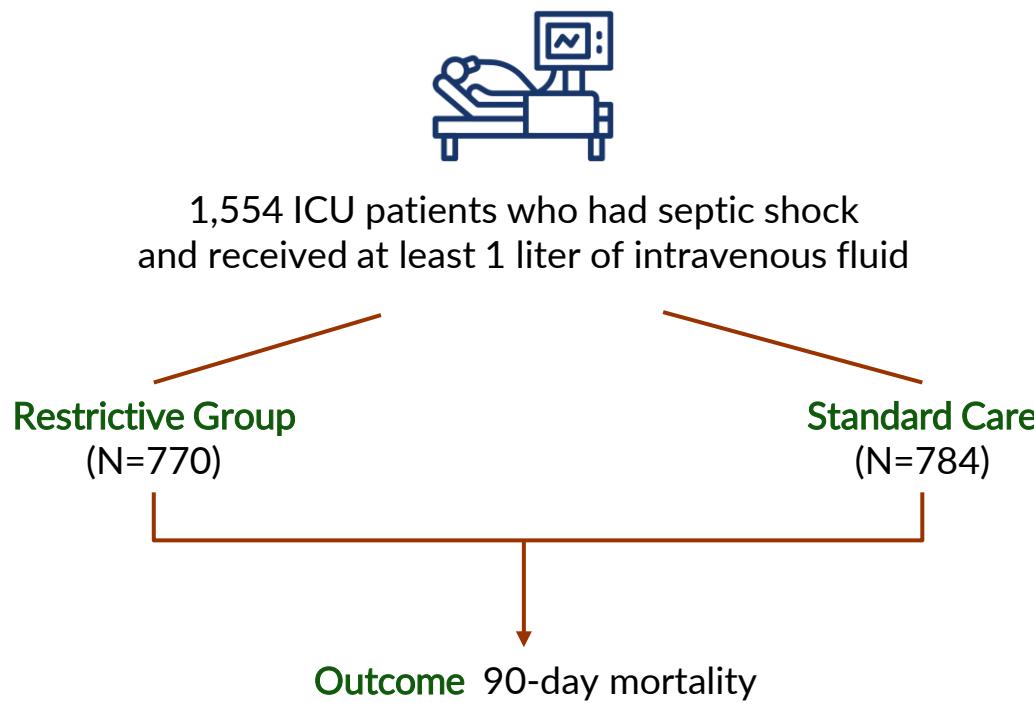
SPLIT	SALT-ED	SMART	BaSICS	PLUS
Other Outcomes				
No different in RRT & 90-d mortality	Lower MAKE30 in balanced solution (4.7% vs 5.6%)	Balanced solution had lower incidence of hyperchloremia and acidemia	Balanced solution had more 90-d mortality in TBI patients	No different in RRT
	Balanced solution had lower incidence of hyperchloremia and acidemia		No different in RRT	Higher chloride level in saline group

Restrictive VS Liberal Fluid Strategies

1 CLASSIC Trial

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

CLASSIC Trial
NEJM, Jun 30, 2022



November 2018 to November 2021

- International, stratified, parallel group, open-label, randomized clinical trial
- 31 ICUs in Denmark, Norway, Sweden, Switzerland, Italy, the Czech Republic, the United Kingdom, and Belgium
- Patients must receipt of at least 1 L of intravenous fluids in the 24 hours before screening & onset of shock had been within 12 hours before screening

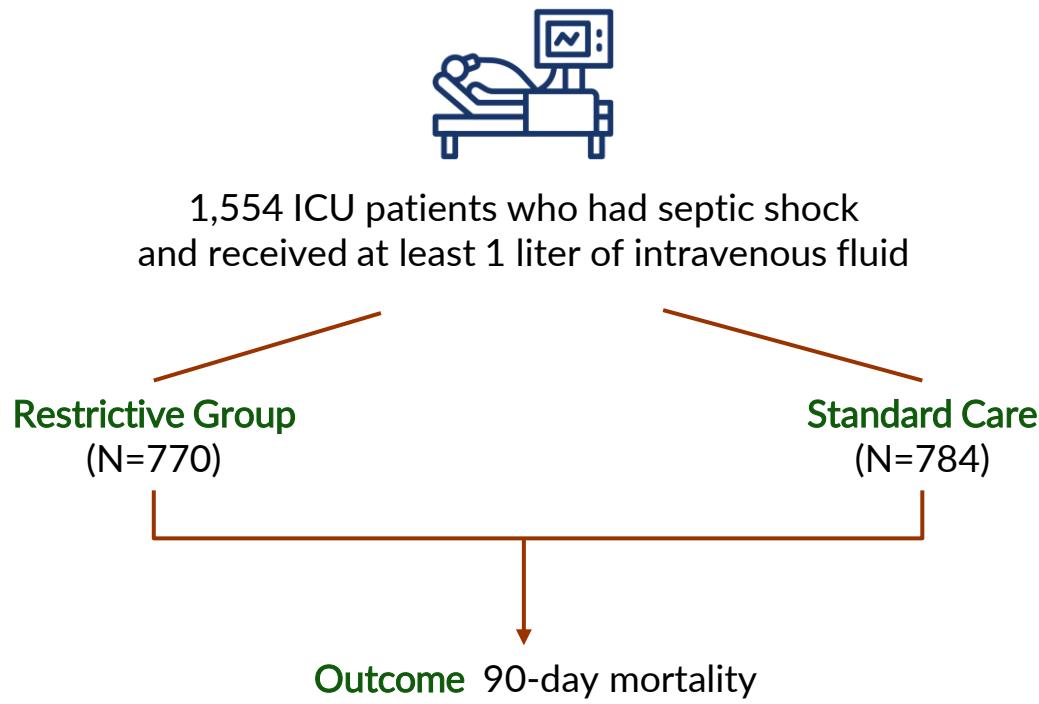
Septic Shock

Defined by Sepsis-3 Criteria

- Suspected or confirmed infection
- Plasma lactate $> 2 \text{ mmol/L}$
- Vasopressor requirement

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

CLASSIC Trial
NEJM, Jun 30, 2022



November 2018 to November 2021

Restrictive Group

IV fluid could only be given under following conditions

1. Severe hypoperfusion
 - Plasma lactate > 4 mmol/L
 - MAP < 50 mmHg despite vasopressor infusion
 - Mottling score > 2
 - Urine output < 0.1 ml/kg/h in first 2 h
-> Isotonic crystalloid 250-500 ml IV bolus
2. To replace documented fluid losses
3. Correct dehydration or electrolyte deficiency when enteral route was contraindicated
4. To ensure a total daily fluid intake of 1 liter

Standard Group

IV fluid could only be given under following conditions

1. As long as the patient had improvement in hemodynamic factors
2. Replace expected or observed losses or to correct dehydration or electrolyte derangements
3. Maintenance fluid if the ICU had a protocol that recommended

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

CLASSIC Trial
NEJM, Jun 30, 2022



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Restrictive-Fluid Group (N=755)	Standard-Fluid Group (N=776)
Median age (IQR) — yr	71 (62–77)	70 (60–77)
Male sex — no. (%)	452 (59.9)	452 (58.2)
Coexisting condition — no. (%)		
Hematologic or metastatic cancer	128 (17.0)	140 (18.0)
Ischemic heart disease or heart failure	116 (15.4)	151 (19.5)
Chronic hypertension	346 (45.8)	360 (46.4)
Long-term dialysis†	9 (1.2)	12 (1.5)
Median time from ICU admission to randomization (IQR) — hr	3 (1–7)	3 (1–8)
Median predicted 90-day mortality (IQR) — %‡	40 (34–50)	40 (31–50)
Source of ICU admission — no. (%)		
Emergency department or prehospital	297 (39.3)	299 (38.5)
Hospital ward	258 (34.2)	300 (38.7)
Operating or recovery room	173 (22.9)	153 (19.7)
Another ICU	27 (3.6)	24 (3.1)
Focus of infection — no. (%)§		
Gastrointestinal	278 (36.8)	297 (38.3)
Pulmonary	209 (27.7)	206 (26.5)
Urinary tract	119 (15.8)	133 (17.1)
Skin or soft tissue	62 (8.2)	64 (8.2)
Other	85 (11.3)	76 (9.8)
Body weight, blood values, and interventions		
Median body weight (IQR) — kg	77 (67–90)	78 (67–91)
Median highest plasma lactate (IQR) — mmol per liter¶	3.8 (2.7–6.0)	3.9 (2.8–6.1)
Median highest dose of norepinephrine (IQR) — µg/kg/min	0.25 (0.12–0.44)	0.23 (0.12–0.41)
Median volume of intravenous fluid 24 hr before randomization (IQR) — ml**	3200 (2000–4700)	3000 (2000–4842)
Use of systemic glucocorticoid — no. (%)	216 (28.6)	226 (29.1)
Median highest plasma creatinine (IQR) — mg/dl††	1.6 (1.1–2.4)	1.6 (1.1–2.5)
Use of respiratory support — no. (%)‡‡	397 (52.6)	377 (48.6)

BASELINE CHARACTERISTICS

- Patient characteristics at baseline were generally well balanced between the two groups
- Patients in both intervention groups remained in the ICU for a median of 5 days
- The most common infection source was GI

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

CLASSIC Trial
NEJM, Jun 30, 2022



Table 2. Cumulative Fluid Volumes and Balances in ICU in the Two Intervention Groups.*

Variable	Restrictive-Fluid Group (N=755)	Standard-Fluid Group (N=776)	Difference (Restrictive vs. Standard) <i>milliliters</i>
Intravenous fluid volume†			
After 1 day‡			
Median (IQR)	500 (0 to 1400)	1,313 (500 to 2500)	-813
Mean	1,024	1,724	-700
After 5 days			
Median (IQR)	1,450 (445 to 3200)	3,077 (1535 to 5300)	-1627
Mean	2,327	3,836	-1509
After 90 days			
Median (IQR)	1,798 (500 to 4366)	3,811 (1861 to 6762)	-2013
Mean	3,414	5,275	-1861
Total fluid volume§			
After 1 day‡			
Median (IQR)	1,843 (964 to 3150)	2,708 (1403 to 4267)	-865
Mean	2,315	3,070	-755
After 5 days			
Median (IQR)	8,864 (4865 to 13,488)	10,800 (6178 to 15,459)	-1936
Mean	9,630	11,181	-1551
After 90 days			
Median (IQR)	10,433 (5024 to 25,567)	12,747 (6453 to 28,110)	-2314
Mean	20,307	23,420	-3113
Cumulative fluid balance¶			
After 1 day‡			
Median (IQR)	725 (0 to 1837)	1,342 (308 to 2759)	-617
Mean	1,100	1,689	-589
After 5 days			
Median (IQR)	1,676 (-137 to 4117)	2,420 (759 to 4996)	-744
Mean	2,297	3,187	-890
After 90 days			
Median (IQR)	1,645 (-461 to 4423)	2,368 (368 to 5517)	-723
Mean	2,302	3,117	-815

FLUID THERAPY

- Median cumulative volume (excluding fluids administered with medication and nutrition)
 - Restrictive group = 1,798 ml
 - Standard group = 3,811 ml
- Median cumulative volume of all fluids given in the ICU
 - Restrictive group = 10,433 ml
 - Standard group = 12,747 ml
- Median cumulative fluid balance
 - Restrictive group = 1,645 ml
 - Standard group = 2,368 ml

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

CLASSIC Trial
NEJM, Jun 30, 2022



Table 3. Primary and Secondary Outcomes.

Outcome	Restrictive-Fluid Group	Standard-Fluid Group	Adjusted Absolute Difference <i>percentage points</i>	Adjusted Relative Risk	P Value
Primary outcome*					
Death by day 90 — no./total no. (%)†	323/764 (42.3)	329/781 (42.1)	0.1 (95% CI, -4.7 to 4.9)	1.00 (95% CI, 0.89 to 1.13)	0.96
Secondary outcomes‡					
Serious adverse events — no./total no. (%)§	221/751 (29.4)	238/772 (30.8)	-1.7 (99% CI, -7.7 to 4.3)	0.95 (99% CI, 0.77 to 1.15)	0.46
Cerebral ischemia	17/755 (2.3)	18/776 (2.3)			
Myocardial ischemia	16/755 (2.1)	6/776 (0.8)			
Intestinal ischemia	41/755 (5.4)	44/776 (5.7)			
Limb ischemia	18/755 (2.4)	18/776 (2.3)			
Severe acute kidney injury	173/750 (23.1)	189/772 (24.5)			
Serious adverse reaction — no./total no. (%)¶	31/755 (4.1)	32/776 (4.1)	-0.1 (99% CI, -2.8 to 2.6)	0.99 (99% CI, 0.50 to 1.93)	0.95
No. of days alive without life support					
Median (IQR)	77 (1 to 87)	77 (1 to 87)	0 (-11 to 11)	—	0.84
Mean	50	51			
No. of days alive and out of the hospital**					
Median (IQR)	21 (0 to 69)	33 (0 to 70)	-12 (-30 to 6)	—	0.84
Mean	33	35			

OUTCOME

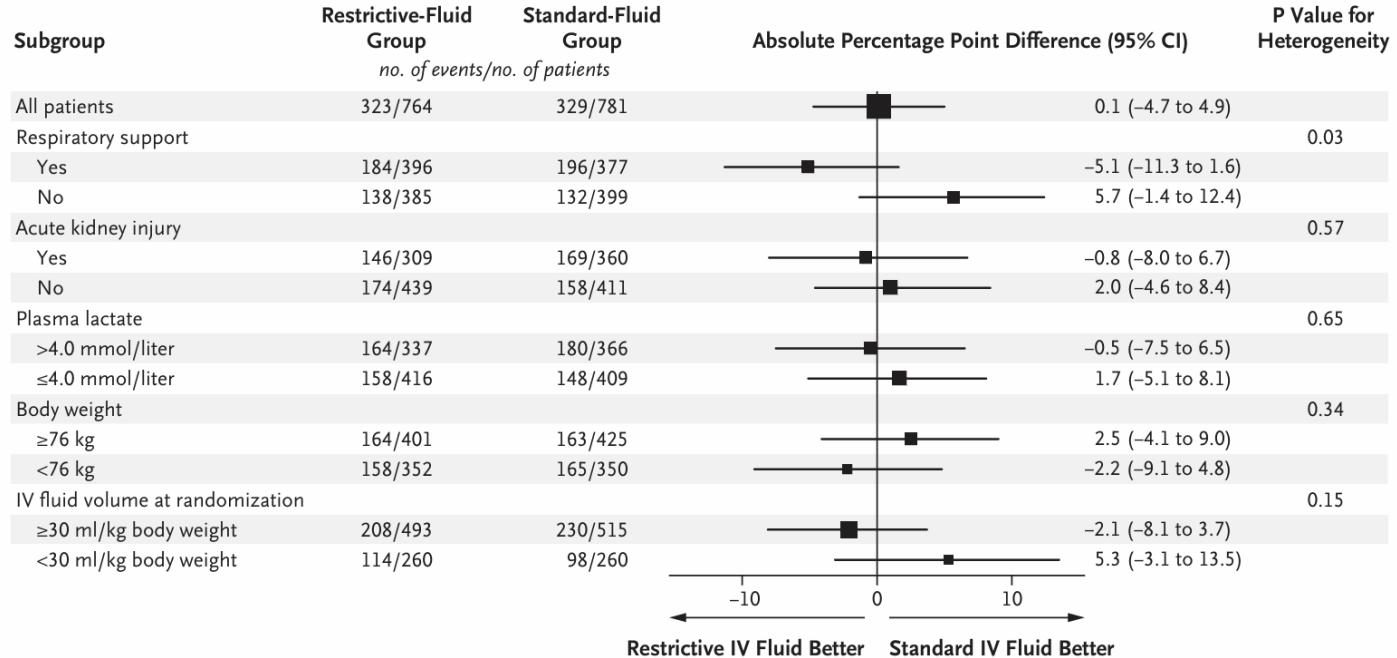
- No significant different in 90-day mortality : 42.3% vs 42.1% (p=0.96)
- No significant difference in no. of serious adverse events, no. of days alive without life support, no. of days alive and out of the hospital

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

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B Death at 90 Days



SUBGROUP ANALYSIS

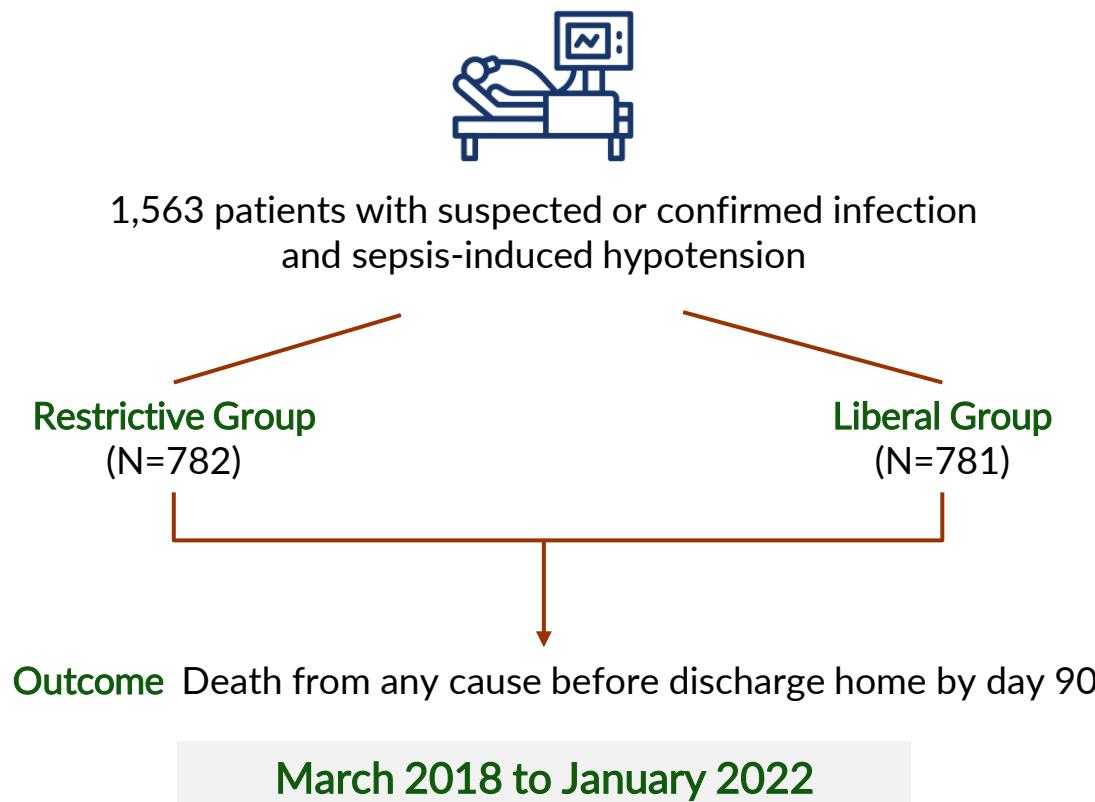
- No statistically significant differences noted in any of pre-specified subgroups

Among adult patients with septic shock in the ICU, *intravenous fluid restriction did not result in fewer deaths* at 90 days than standard intravenous fluid therapy

2 CLOVERS Trial

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
NEJM, Feb 9, 2023



- Multicenter, randomized, unblinded superiority trial
- 60 centers in US
- Assigned protocol was followed for a period of 24h

Suspected or confirmed infection

Administration or planned administration of antibiotic agents

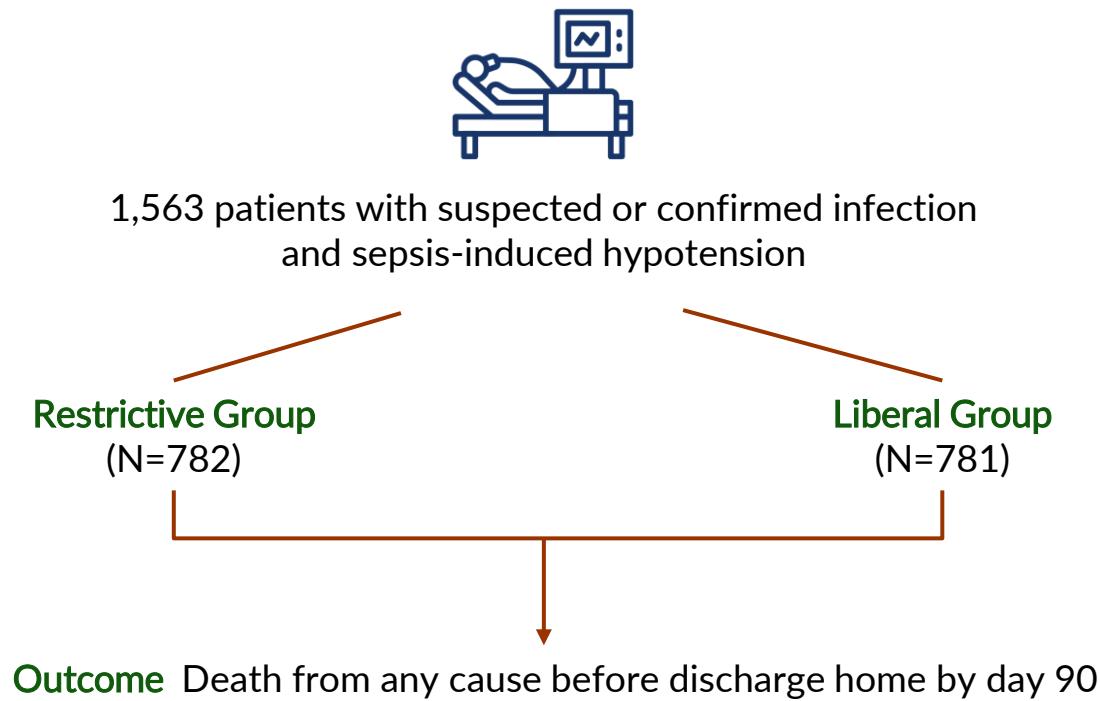
Sepsis induced hypotension

SBP <100 mmHg after administration of $\geq 1,000$ ml of IV fluid

Excluded patients who previous receipt of ≥ 3000 ml of intravenous fluid during this episode (including prehospital administration)

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
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Restrictive Fluid Group

- Prioritized vasopressors as the primary treatment
- “Rescue fluids” being permitted for prespecified indications

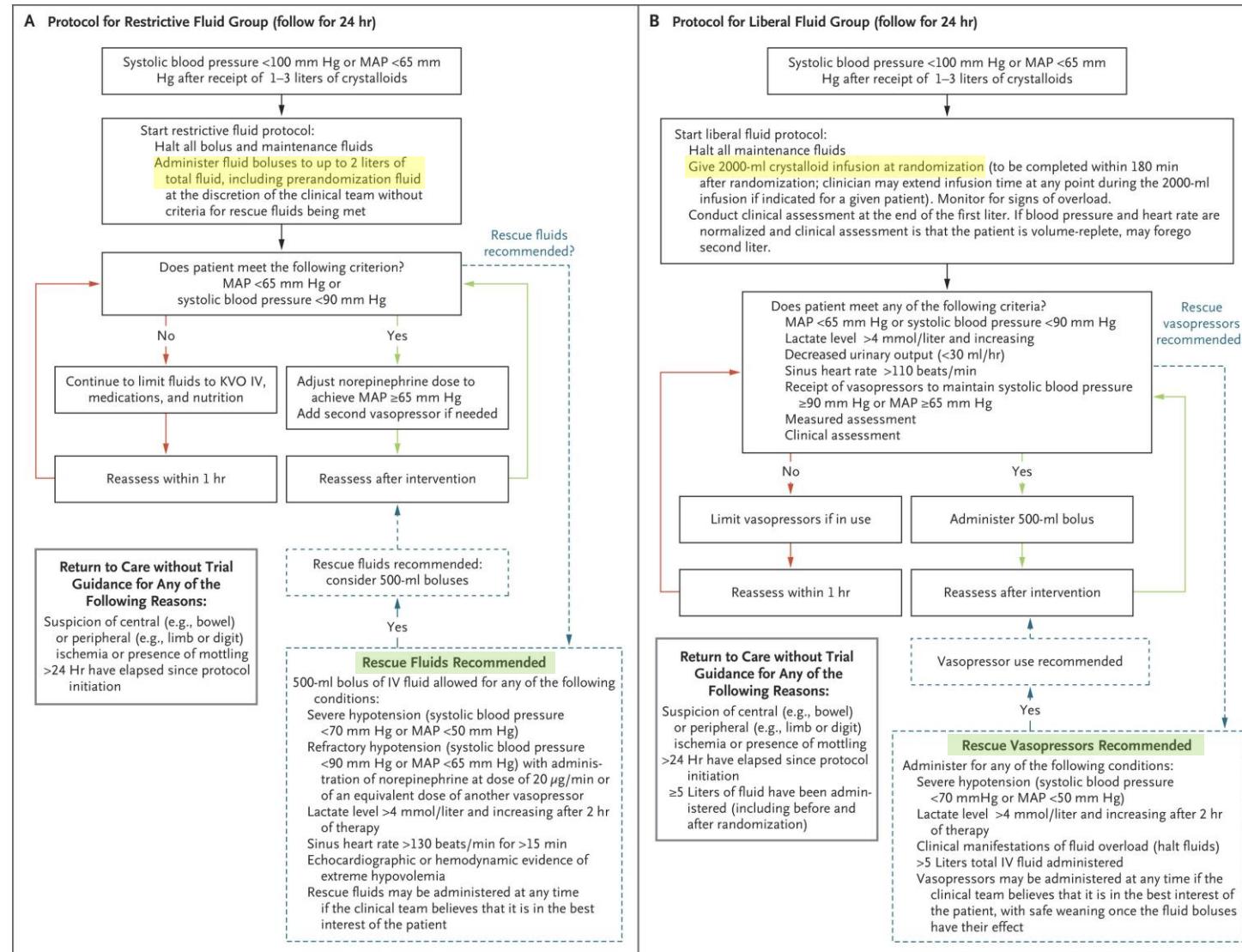
Liberal Fluid Group

- Recommended initial 2000-ml intravenous infusion of isotonic crystalloid
- Followed by fluid boluses administered on the basis of clinical triggers
- “Rescue vasopressors” permitted for prespecified indications

March 2018 to January 2022

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
NEJM, Feb 9, 2023



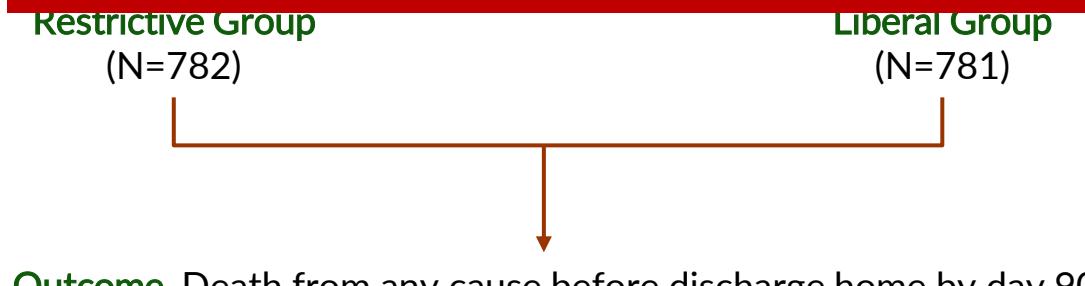
Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
NEJM, Feb 9, 2023



- Estimated that a total sample of 2,320 patients would need to detect an absolute between-group difference of 4.5 percentage points in the incidence of death before discharge home by day 90

EARLY TERMINATION DURING 2nd INTERIM ANALYSIS



Outcome Death from any cause before discharge home by day 90

March 2018 to January 2022

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
NEJM, Feb 9, 2023



Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Restrictive Fluid Group (N=782)	Liberal Fluid Group (N=781)	Total (N=1563)
Age — yr	59.1±16.0	59.9±15.9	59.5±15.9
Female sex — no. (%)	371 (47.4)	366 (46.9)	737 (47.2)
Race — no. (%)†			
White	534 (68.3)	571 (73.1)	1105 (70.7)
Black	135 (17.3)	112 (14.3)	247 (15.8)
Asian	28 (3.6)	26 (3.3)	54 (3.5)
Other	10 (1.3)	6 (0.8)	16 (1.0)
Not reported	78 (10.0)	67 (8.6)	145 (9.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	118 (15.1)	108 (13.8)	226 (14.5)
No	628 (80.3)	646 (82.7)	1274 (81.5)
Not reported	36 (4.6)	27 (3.5)	63 (4.0)
Coexisting conditions — no./total no. (%)			
Diabetes	222/777 (28.6)	224/773 (29.0)	446/1550 (28.8)
Chronic heart failure	99/777 (12.7)	79/773 (10.2)	178/1550 (11.5)
End-stage renal disease treated with hemodialysis	33/777 (4.2)	40/773 (5.2)	73/1550 (4.7)
SOFA score‡	3.4±2.8	3.5±2.7	3.4±2.7
Systolic blood pressure — mm Hg	93.2±12.0	93.8±12.2	93.5±12.1
Median time from meeting trial eligibility criteria to randomization (IQR) — min	61 (26–116)	60 (25–117)	61 (26–116)
Location at randomization — no. (%)			
Emergency department	729 (93.2)	708 (90.7)	1437 (91.9)
ICU	44 (5.6)	62 (7.9)	106 (6.8)
Other	9 (1.2)	11 (1.4)	20 (1.3)
Median volume of fluid administered before randomization (IQR) — ml	2050 (1500–2457)	2050 (1371–2442)	2050 (1450–2450)

BASELINE CHARACTERISTICS

- Patients in the two groups were similar at baseline
- Most common primary source of infection is pneumonia
- Patients in both groups received similar volumes of intravenous fluid before randomization (median 2,050 ml in both group)
- Patients receiving vasopressors at randomization was similar: 21% in the restrictive fluid group & 18% in the liberal fluid group

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
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Table 2. Therapies Administered during the Trial Intervention Period.*

Therapies	Restrictive Fluid Group (N=782)	Liberal Fluid Group (N=781)	Difference (95% CI)†
Median volume of IV fluid administered (IQR) — ml‡			
Over 6-hr period	500 (130 to 1097)	2300 (2000 to 3000)	-1800 (-1889 to -1711)
Over 24-hr period	1267 (555 to 2279)	3400 (2500 to 4495)	-2134 (-2318 to -1949)
Vasopressor administration during first 24-hr period — no./total no. (%)	460/780 (59.0)	290/779 (37.2)	21.7 (16.9 to 26.6)
Time from randomization to first vasopressor among patients who had vasopressors administered — hr§	1.8±3.4	3.2±4.7	-1.4 (-2.0 to -0.8)
Duration of vasopressor use during first 24-hr period among patients who received vasopressor therapy — hr¶	9.6±10.0	5.4±8.6	4.2 (3.3 to 5.2)

THERAPY

- Cumulative median volume of fluid administered during the 6 and 24 hours was lower in the restrictive fluid group
- Vasopressors were more commonly used, initiated earlier, and used for longer in the restrictive fluid group
- Lactated Ringer's solution was the most common type of fluid administered

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
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Table 3. Outcomes.*

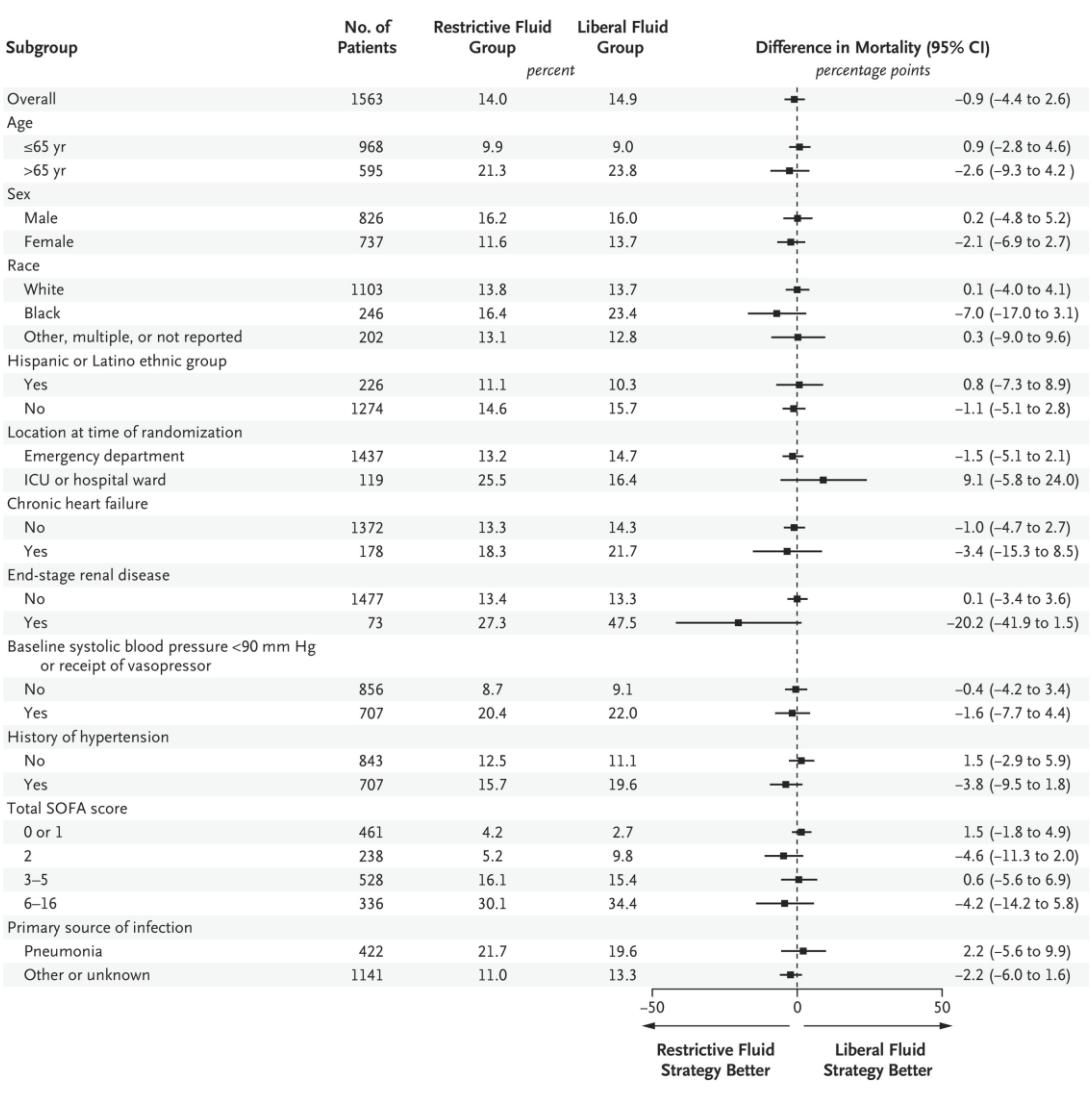
Outcome	Restrictive Fluid Group (N=782)		Liberal Fluid Group (N=781)		Difference (95% CI)†
	No. of Patients	Mean (95% CI)	No. of Patients	Mean (95% CI)	
Death before discharge home by day 90 — % of patients‡	782	14.0 (11.6 to 16.4)	781	14.9 (12.4 to 17.4)	-0.9 (-4.4 to 2.6)§
No. of days free from organ-support therapy at 28 days	778	24.0 (23.4 to 24.6)	778	23.6 (23.0 to 24.3)	0.3 (-0.5 to 1.2)
No. of days free from ventilator use at 28 days	773	23.4 (22.7 to 24.1)	771	22.8 (22.0 to 23.5)	0.6 (-0.4 to 1.6)
No. of days free from renal-replacement therapy at 28 days	737	24.1 (23.4 to 24.8)	738	23.9 (23.2 to 24.6)	0.2 (-0.8 to 1.2)
No. of days free from vasopressor use at 28 days¶	778	22.0 (21.4 to 22.7)	778	21.6 (20.9 to 22.3)	0.4 (-0.5 to 1.3)
No. of days out of the ICU from day 1 to day 28	778	22.8 (22.2 to 23.4)	778	22.7 (22.0 to 23.3)	0.1 (-0.8 to 1.0)
No. of days out of the hospital by day 28	778	16.2 (15.4 to 17.0)	778	15.4 (14.6 to 16.2)	0.8 (-0.3 to 1.9)
New intubation with invasive mechanical ventilation by 28 days — no. of patients (%)	701	77 (11.0)	687	87 (12.7)	-1.7 (-5.1 to 1.7)
Initiation of renal-replacement therapy by 28 days — no. of patients (%)	738	24 (3.3)	738	24 (3.3)	0.0 (-1.8 to 1.8)
KDIGO score on day 3	585	0.35 (0.28 to 0.41)	604	0.34 (0.28 to 0.41)	0.0 (-0.1 to 0.1)
Change in SOFA score from baseline to 72 hr	619	-0.7 (-0.9 to -0.4)	634	-0.8 (-1.0 to -0.5)	0.1 (-0.3 to 0.4)
Death from any cause at any location by day 90 — no. of patients (%)	768	172 (22.4)	773	169 (21.9)	0.5 (-3.6 to 4.7)
ARDS onset between day 1 and day 7 — no. of patients (%)	757	19 (2.5)	758	20 (2.6)	-0.1 (-1.7 to 1.5)
New-onset atrial or ventricular arrhythmia to day 28 — no. of patients (%)	779	59 (7.6)	778	67 (8.6)	-1.0 (-3.7 to 1.7)
Severe adverse event — no. of events**	782	21	781	19	2 (-10 to 14) ††

OUTCOME

- No significant difference in death before discharge home by day 90 between two groups : 14.0% vs 14.9% (estimated difference -0.9%, p=0.61)
- No significant difference in other efficacy and safety outcomes

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

CLOVERS Trial
NEJM, Feb 9, 2023



SUBGROUP ANALYSIS

- No subgroup favored with liberal or restrictive fluid use

Among patients with sepsis-induced hypotension, the ***restrictive fluid strategy did not result in significantly lower (or higher) mortality*** before discharge home by day 90 than the liberal fluid strategy

Comparison of Fluid Balance Studies

	CLASSIC	CLOVERS
Location	Europe	US
Population	1554	1563
Protocol		
Patients	ICU patients: septic shock	ICU patients: septic shock
Intervention	Restrictive fluid	Restrictive fluid
Control	Standard care	Liberal fluid

Comparison of Fluid Balance Studies

	SPLIT	SALT-ED
Primary Outcome		
Primary outcome	90-d mortality	Death before discharge home by day 90
Intervention	42.3%	14.0%
Control	42.1%	14.9%

Personalized Resuscitation

1 ANDROMEDA-SHOCK-2 Trial

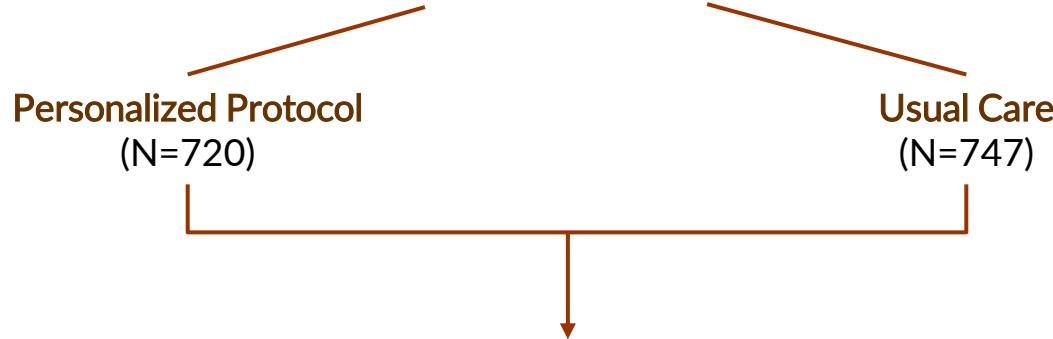
Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

The ANDROMEDA-SHOCK-2 Randomized Clinical Trial

ANDROMEDA-SHOCK-2 Trial
JAMA, Oct 29, 2025



1,467 patients with early septic shock



- ANDROMEDA-SHOCK trial (2019)
: CRT-targeted resuscitation was associated with faster recovery of organ dysfunction, less fluid administration, and higher likelihood of survival compared with lactate-targeted resuscitation
- Multicenter, randomized clinical trial
- 86 intensive care units across countries from the Americas, Europe, and Asia

Outcome Hierarchical composite of 28-day mortality, duration of vital support and length of hospital stay

March 2022 to April 2025

Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

The ANDROMEDA-SHOCK-2 Randomized Clinical Trial

ANDROMEDA-SHOCK-2 Trial
JAMA, Oct 29, 2025



1,467 patients with early septic shock

Personalized Protocol
(N=720)

Usual Care
(N=747)

Outcome Hierarchical composite of 28-day mortality, duration of vital support and length of hospital stay

March 2022 to April 2025

Septic Shock Definition

Based on Sepsis-3 criteria

Personalized hemodynamic resuscitation protocol targeting capillary refill time (CRT-PHR)

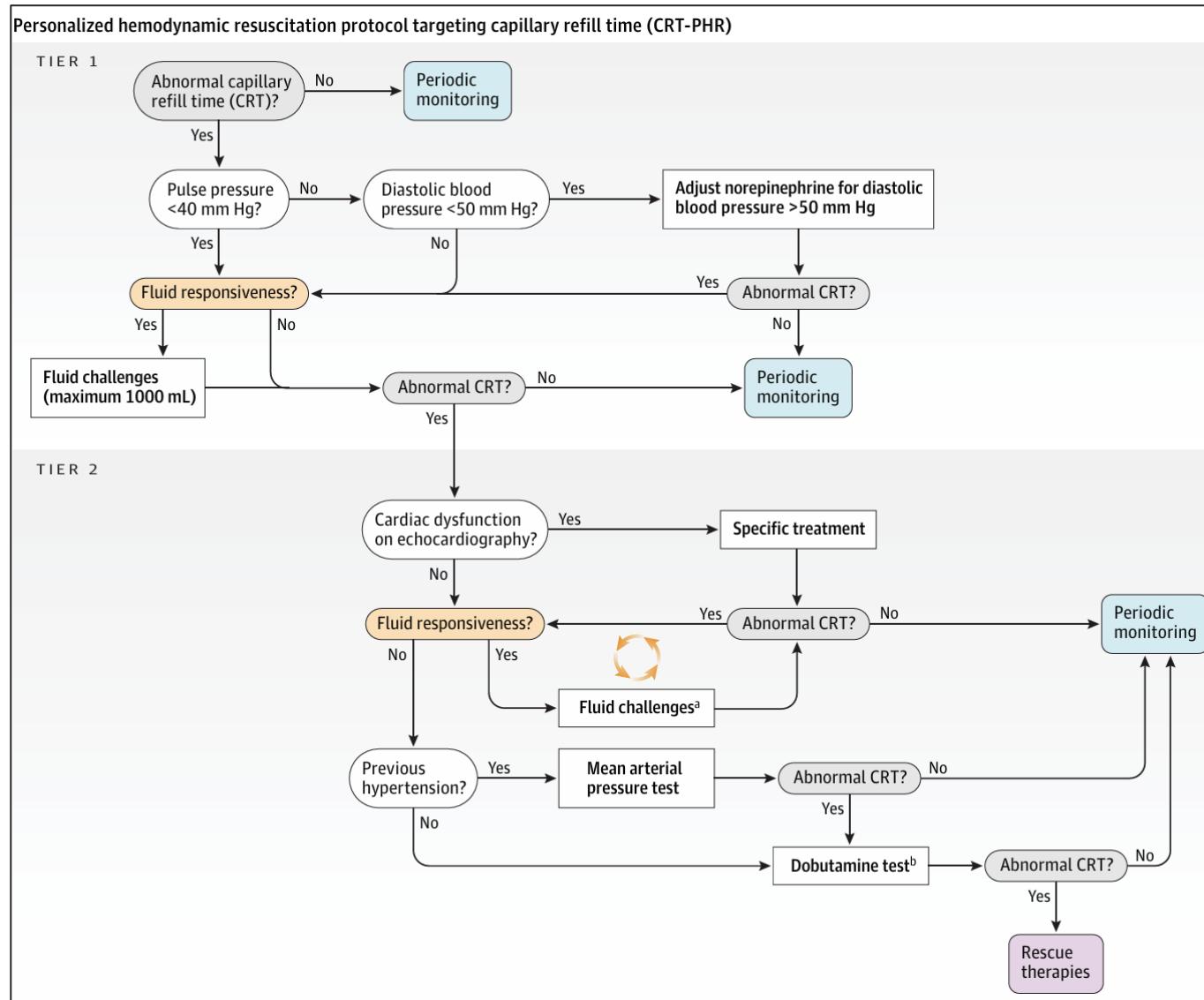
- = 6-hour study period aimed at normalizing CRT
1. CRT normalization as the target of resuscitation
 2. Baseline identification of individual hemodynamic patterns of cardiovascular dysfunction
 3. Systematic fluid-responsiveness assessment
 4. 2 acute (1 hour) hemodynamic tests

Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

ANDROMEDA-SHOCK-2 Trial

JAMA, Oct 29, 2025

The ANDROMEDA-SHOCK-2 Randomized Clinical Trial



Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

The ANDROMEDA-SHOCK-2 Randomized Clinical Trial

ANDROMEDA-SHOCK-2 Trial
JAMA, Oct 29, 2025

Characteristic	No./total No. (%)	
	CRT-PHR group (n = 720)	Usual care group (n = 747)
Age, median (IQR), y	66.0 (52.0-74.0)	65.0 (51.0-76.0)
Sex, No. (%)		
Female	302 (41.9)	334 (44.7)
Male	418 (58.1)	413 (55.3)
Weight, median (IQR) [total No.], kg	70.0 (60.0-80.0) [n = 717]	70.0 (60.4-80.0) [n = 747]
Severity scores, median (IQR)		
APACHE II ^a	19.0 (14.0-24.0)	18.0 (13.0-23.0)
SOFA [total No.] ^b	8.0 (7.0-11.0) [n = 719]	8.0 (7.0-10.0) [n = 745]
Charlson Comorbidity Index ^c	4.0 (2.0-5.0)	3.0 (2.0-5.0)
Comorbidities		
Chronic hypertension	162/705 (23.0)	179/730 (24.5)
Diabetes	167/706 (23.7)	161/731 (22.0)
Chronic pulmonary disease	81/703 (11.5)	65/730 (8.9)
Diabetes with chronic complications	58/701 (8.3)	47/726 (6.5)
Nonhematological cancer	46/702 (6.6)	30/727 (4.1)
Hematological cancer	12/700 (1.7)	21/726 (2.9)
Source of infection		
Abdominal	350/717 (48.8)	343/745 (46.0)
Respiratory	126/717 (17.6)	156/745 (20.9)
Urinary	151/717 (21.1)	131/745 (17.6)
Cutaneous and soft tissue	42/717 (5.9)	55/745 (7.4)
Bloodstream	27/717 (3.8)	39/745 (5.2)
Bone and joint	5/717 (0.7)	7/745 (0.9)
Central nervous system	6/717 (0.8)	5/745 (0.7)
Mediastinitis	6/717 (0.8)	4/745 (0.5)
Other ^d	4/717 (0.6)	5/745 (0.7)

Characteristic	No./total No. (%)	
	CRT-PHR group (n = 720)	Usual care group (n = 747)
Microbiologically confirmed infection ^e	454/707 (64.2)	470/741 (63.4)
Time from meeting septic shock criteria to randomization, median (IQR), h	2 (1-3)	2 (1-3)
Organ support at baseline		
Respiratory		
None	82/719 (11.4)	93/741 (12.6)
Low-flow oxygen	221/719 (30.7)	213/741 (28.7)
High-flow nasal cannula	56/719 (7.8)	52/741 (7.0)
Noninvasive mechanical ventilation	23/719 (3.2)	18/741 (2.4)
Invasive mechanical ventilation	337/719 (46.9)	365/741 (49.3)
Cardiovascular		
Norepinephrine	720/720 (100.0)	747/747 (100.0)
Vasopressin	166/701 (23.7)	149/726 (20.5)
Epinephrine	8/700 (1.1)	13/726 (1.8)
Dobutamine	8/701 (1.1)	5/726 (0.7)
Other ^f	1/701 (0.1)	2/726 (0.3)

Characteristic	No./total No. (%)	
	CRT-PHR group (n = 720)	Usual care group (n = 747)
Hemodynamic- and perfusion-related variables		
Intravenous fluid loading, median (IQR), mL ^g	1500 (1000-2000)	1500 (1000-2000)
Intravenous fluid loading per weight, median (IQR), mL/kg	22.1 (14.3-30.8)	21.4 (14.7-30.4)
Mean arterial pressure, median (IQR), mm Hg	69 (64-76)	69 (65-76)
Heart rate, median (IQR), beats/min	102 (89-116)	105 (89-117)
Norepinephrine dose, median (IQR), µg/kg/min	0.23 (0.12-0.40)	0.21 (0.10-0.39)
Serum lactate, median (IQR), mmol/L	3.7 (2.7-5.5)	3.6 (2.7-5.3)
Serum lactate >4.0 mmol/L, No. (%)	315 (43.8)	314 (42.0)
Capillary refill time, median (IQR) [total No.], s	4.0 (2.4-5.7) [n = 719]	4.0 (3.0-6.0) [n = 742]
Capillary refill time >3 s, No. (%)	419/719 (58.3)	459/742 (61.9)
Venous-to-arterial carbon dioxide difference, median (IQR) [total No.], mm Hg	6.8 (4.4-9.0) [n = 620]	6.3 (4.1-9.0) [n = 616]
Venous-to-arterial carbon dioxide difference >6 mm Hg	324/620 (52.3)	314/628 (51.0)
Central venous oxygen saturation, median (IQR) [total No.], %	74 (67-81) [n = 626]	73 (66-79) [n = 630]
Central venous oxygen saturation <75%	330/626 (52.7)	362/630 (57.5)

BASELINE CHARACTERISTICS

- Patients in the two groups were similar at baseline
- Most common primary source of infection was GI
- Median IV fluid loading = 1,500 ml (~22 ml/kg)

Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

The ANDROMEDA-SHOCK-2 Randomized Clinical Trial

ANDROMEDA-SHOCK-2 Trial
JAMA, Oct 29, 2025

Table 2. Hemodynamic Therapies and Resuscitation-Related Variables at Hour 6

	CRT-PHR group	Usual care group	Absolute difference (95% CI)
Therapy			
Norepinephrine, No./total No. (%)	648/684 (94.7)	634/694 (91.4)	3.4 (0.7 to 6.1)
Norepinephrine dose, mean (SD), µg/r/kg/min [n = 655]	0.28 (0.34) [n = 655]	0.27 (0.41) [n = 634]	-0.01 (-0.05 to 0.03)
Vasopressin, No./total No. (%)	251/684 (36.7)	229/694 (33.0)	3.7 (-1.3 to 8.7)
Dobutamine, No./total No. (%)	84/684 (12.3)	37/694 (5.3)	7.0 (4.0 to 9.9)
Volume of resuscitation fluids, mean (SD), mL [n = 672]	595 (679) [n = 672]	847 (832) [n = 676]	-251 (-316 to -187)
Net fluid balance, mean (SD), mL [n = 629]	990 (1016) [n = 629]	1227 (1225) [n = 622]	-242 (-385 to -99)
Hemodynamic and perfusion-related variable			
Central venous pressure, mean (SD), mm Hg [n = 541]	9.1 (4.1) [n = 541]	9.8 (4.8) [n = 544]	-0.6 (-1.1 to -0.1)
Mean arterial pressure, mean (SD), mm Hg [n = 682]	74.1 (9.4) [n = 682]	73.6 (9.0) [n = 690]	0.6 (-0.5 to 1.7)
Capillary refill time, mean (SD), s [n = 679]	2.8 (1.4) [n = 679]	3.4 (1.9) [n = 684]	-0.6 (-0.7 to -0.4)
Lactate level, mean (SD), mmol/L [n = 659]	3.2 (2.4) [n = 659]	3.5 (3.0) [n = 664]	-0.3 (-0.5 to -0.1)
Central venous oxygen saturation, mean (SD), % [n = 588]	74.4 (8.9) [n = 588]	72.4 (9.9) [n = 596]	1.9 (0.8 to 3.0)

THERAPY

- CRT-PHR group received less resuscitation fluids, received more dobutamine, had lower central venous pressure, and had lower lactate levels
- Patients with normal CRT at baseline who were randomized to the CRT-PHR group had less fluid-responsiveness assessments and received less resuscitation fluids

Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

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Table 3. Primary and Secondary Outcomes

Outcome	CRT-PHR group (n = 720)	Usual care group (n = 747)	Effect estimate (95% CI)	P value
Primary outcome through 28 d, total No. of wins (%)				
Hierarchical composite of death, duration of vital support, and length of hospital stay ^a	131 131 (48.9)	112 787 (42.1)	SWR, 1.16 (1.02 to 1.33)	.04
Secondary outcomes				
All-cause mortality within 28 d, No. (%) ^b	191 (26.5)	199 (26.6)	HR, 0.99 (0.81 to 1.21)	.91
Vital support-free days within 28 d ^c				
Mean (SD)	16.5 (11.3)	15.4 (11.4)	pOR, 1.28 (1.06 to 1.54)	NA
Median (IQR)	23.0 (0 to 25.0)	22.0 (0 to 25.0)		
Length of hospital stay up to day 28, d ^d				
Mean (SD)	15.3 (9.0)	16.2 (9.4)	MD, -0.85 (-1.80 to 0.10)	NA
Median (IQR)	13.0 (8.0 to 25.0)	15.0 (8.0 to 28.0)		

OUTCOME

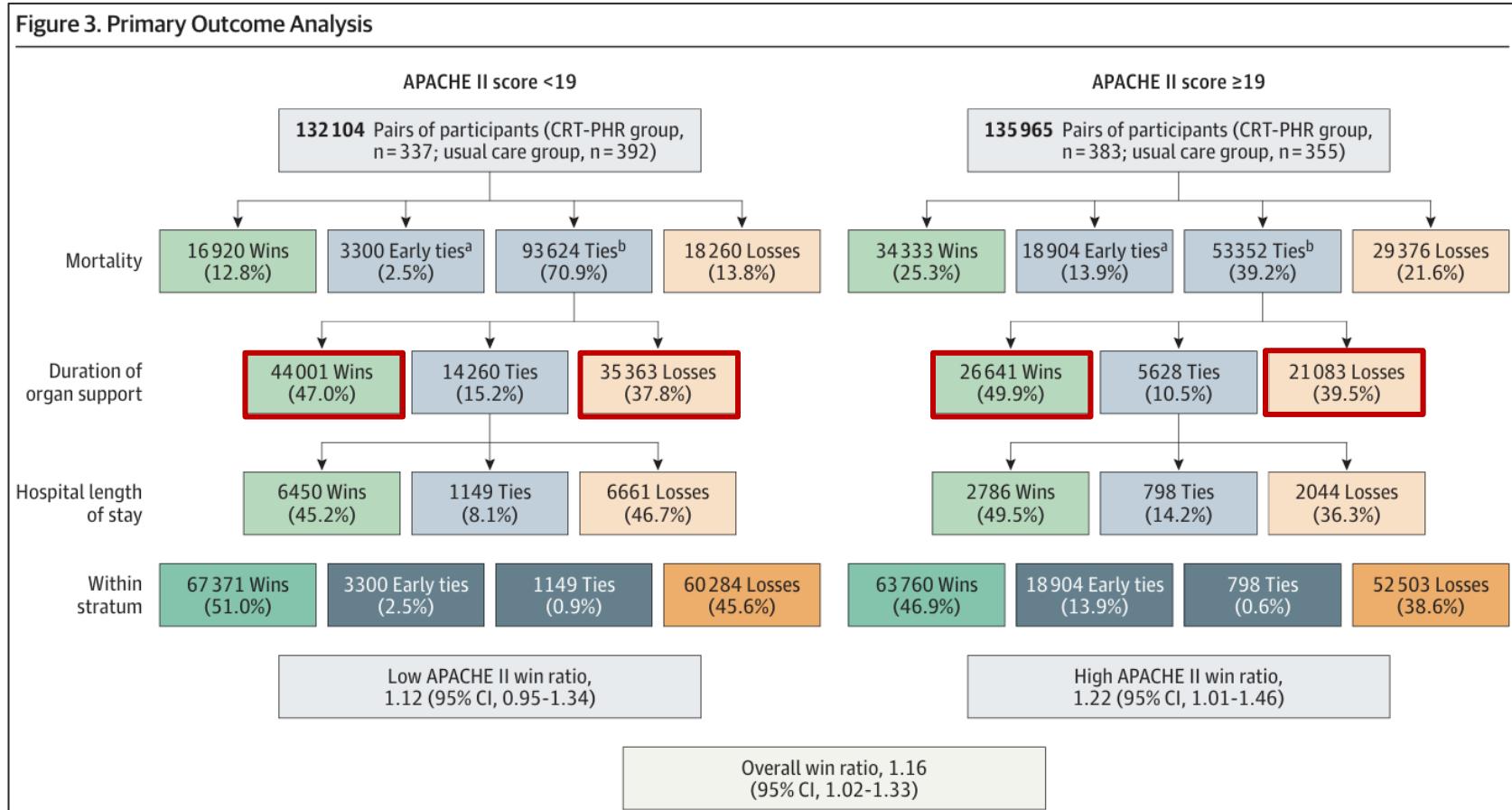
- 131,131 wins (48.9%) for the CRT-PHR group over 112,787 (42.1%) in the usual care group, stratified win ratio of 1.16 (p=0.04)
 - Duration of vital support yielded the highest number of wins to losses: 26.4% vs 21.1%
- Patients in the CRT-PHR group had a higher number of mean organ support-free days within 28 days

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Figure 3. Primary Outcome Analysis



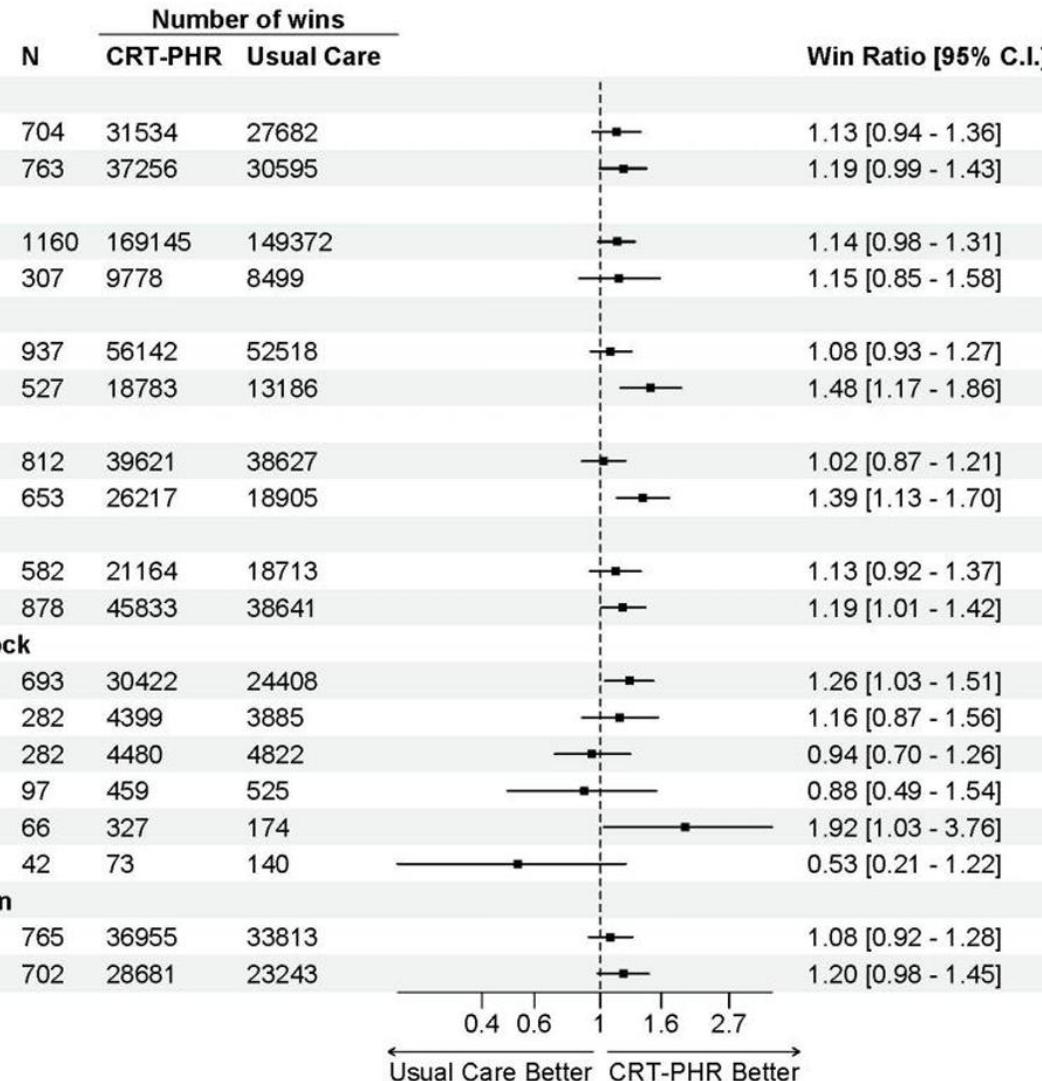
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SUBGROUP ANALYSIS

- No effect modification for the subgroups assessed

Among patients with early septic shock, *a personalized hemodynamic resuscitation protocol*/targeting capillary refill time was *superior to usual care* for the primary composite outcome, primarily due to a lower duration of vital support



THE
END