Fluid Resuscitation in Sepsis

What the heck are we supposed to do now!?

Nick Johnson, MD

Associate Professor

Department of Emergency Medicine

Division of Pulmonary, Critical Care, and Sleep Medicine

Harborview Medical Center/University of Washington

Disclosures

Funding:
NIH, CDC, DoD, UW Royalty Research Fund

CLOVERS Site Principal Investigator

Scientific Advisory Boards:
Opticyte, Inc. & Neuroptics, Inc.

@NickJohnsonMD


Fluid = Drug

Objectives

1. Synthesize the existing data on **fluid type**

2. Discuss the literature on optimal **fluid volume** and **timing** in early sepsis resuscitation

3. Build an **approach** to fluid resuscitation in sepsis


Fluid Flavors

SMART & SALT-ED

Pragmatic, cluster-randomized trial

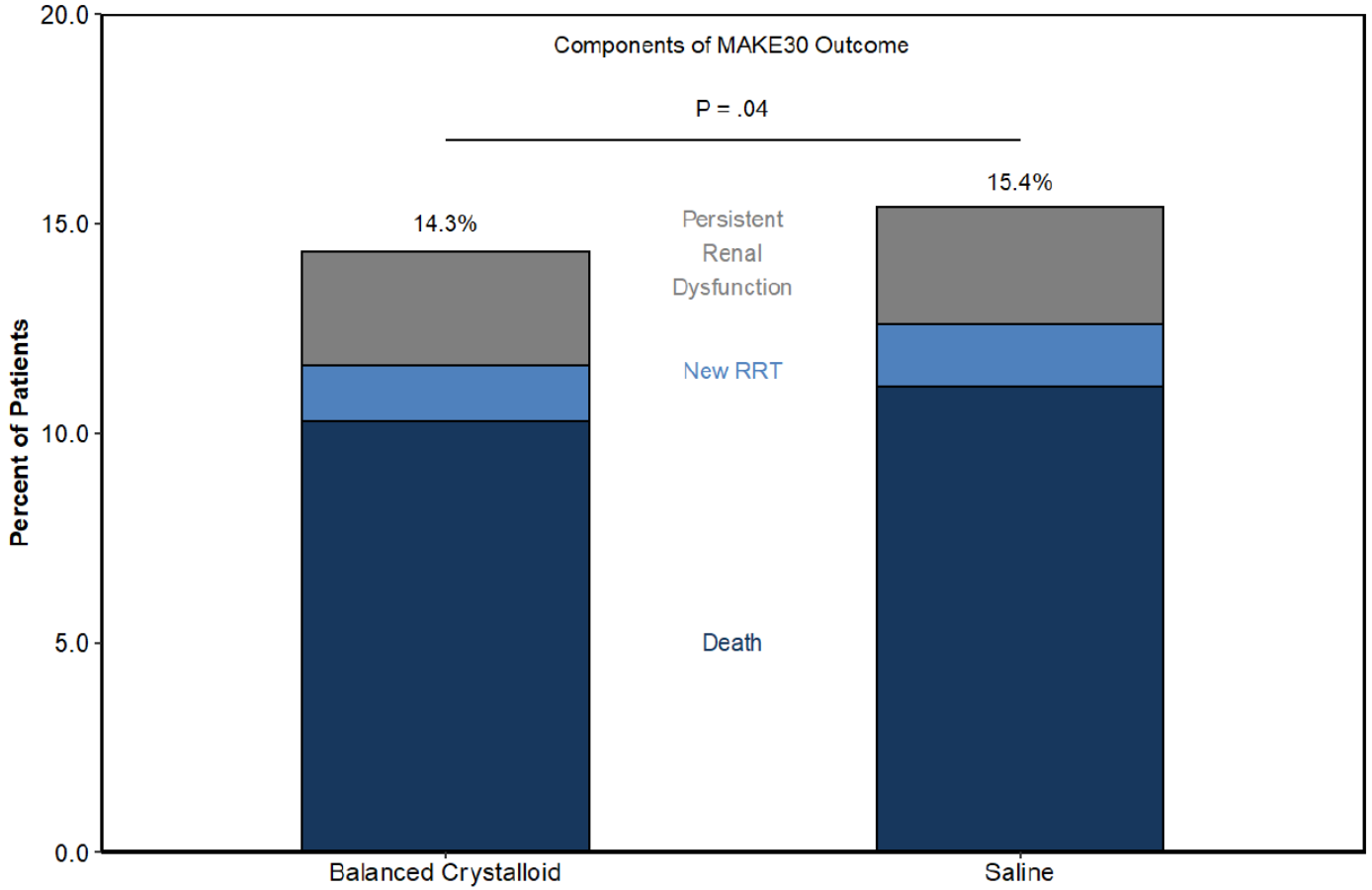
Single center

>15,000 patients

Balanced fluid vs. saline

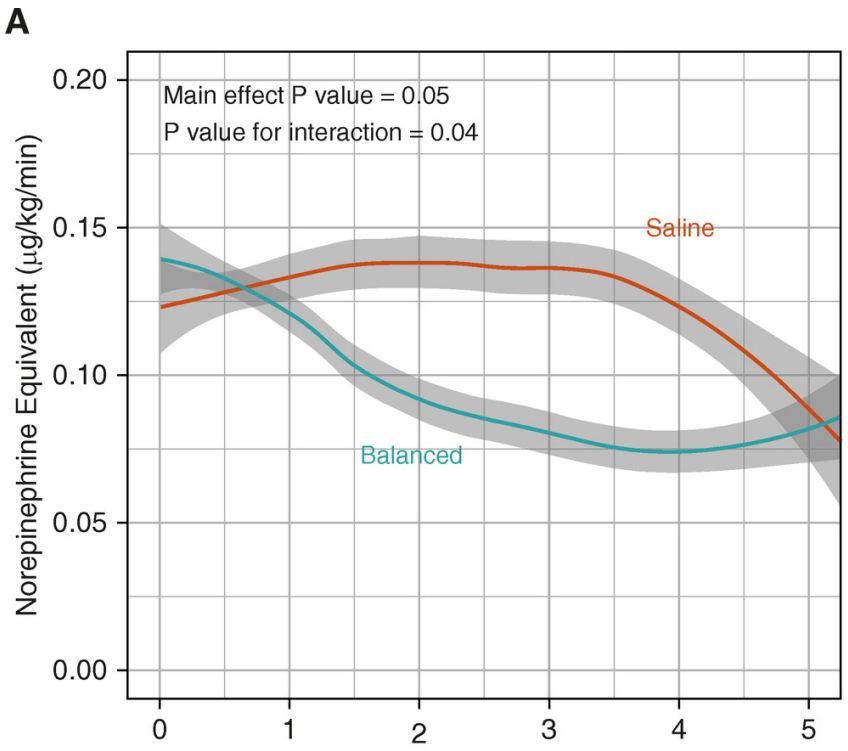
Median fluid volume: 1L

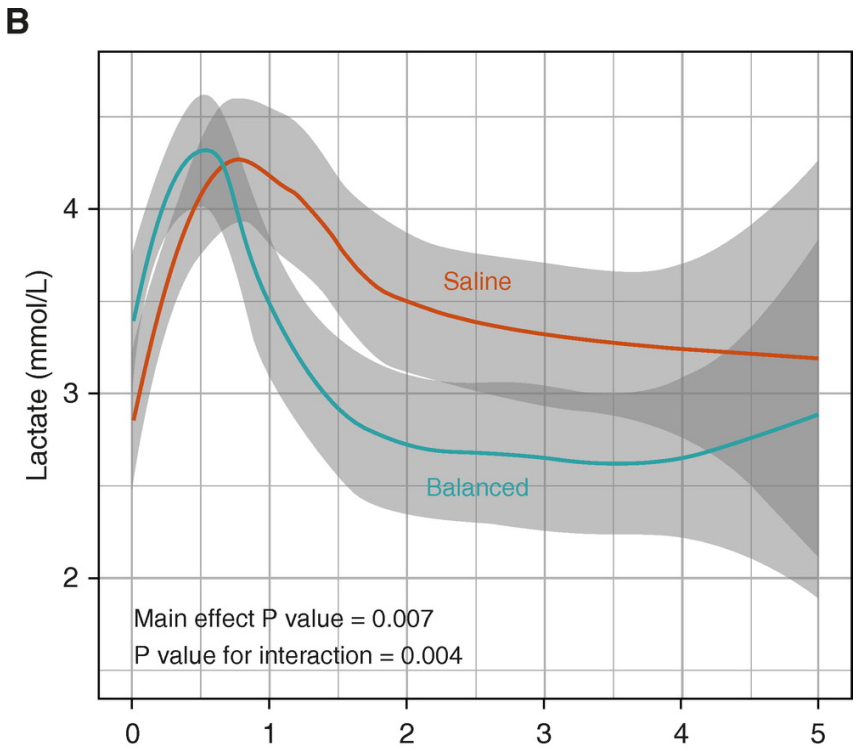
Little contamination



Semler et al. & Self et al. *NEJM* 2018

SMART Sepsis





Sepsis Subgroup (N=1641)

- MAKE-30
  - Saline: 40%
  - Balanced: 35%
- 30-day mortality
  - Saline: 31%
  - Balanced: 26%

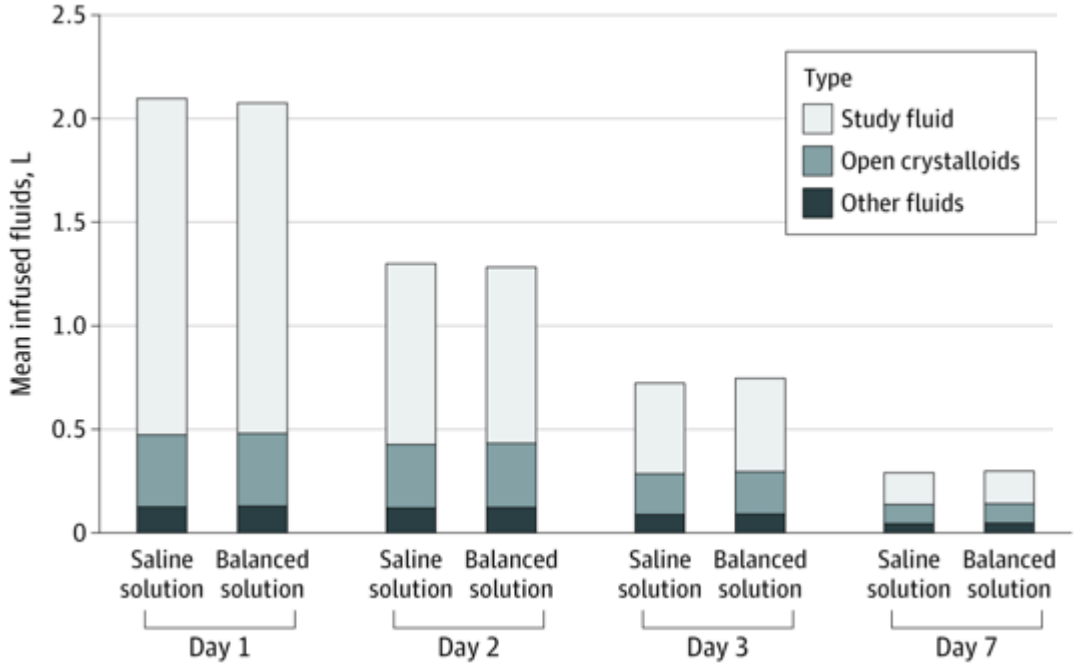
Brown et al. *AJRCCM* 2019

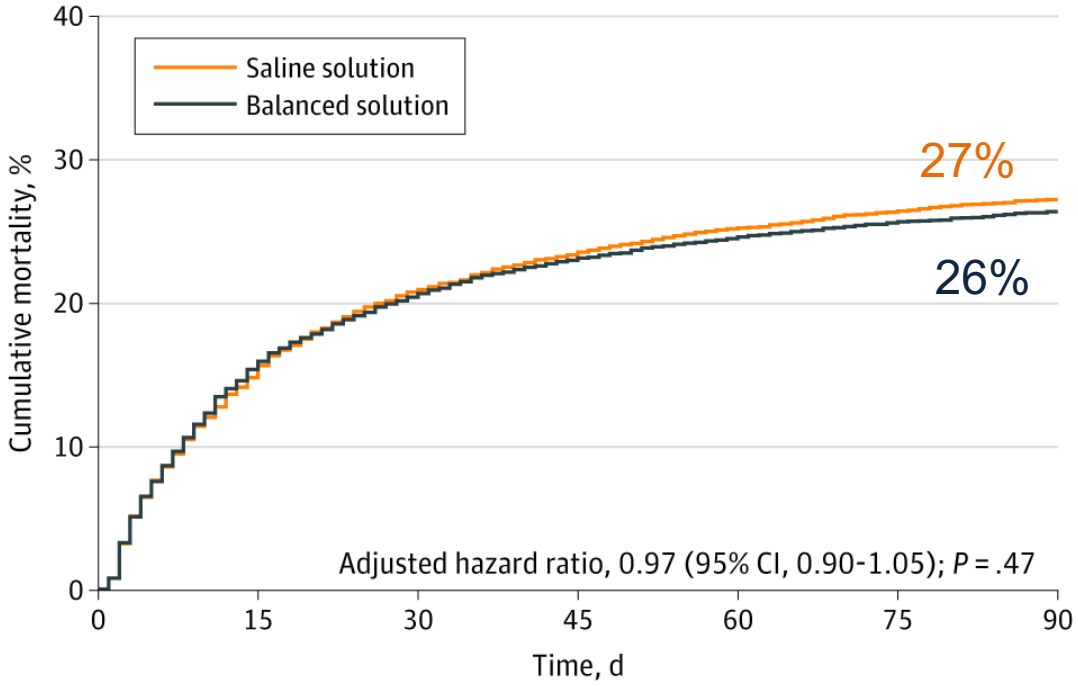
BaSICS Trial

11,051 patients; 75 ICUs

4.1L over first 3 days

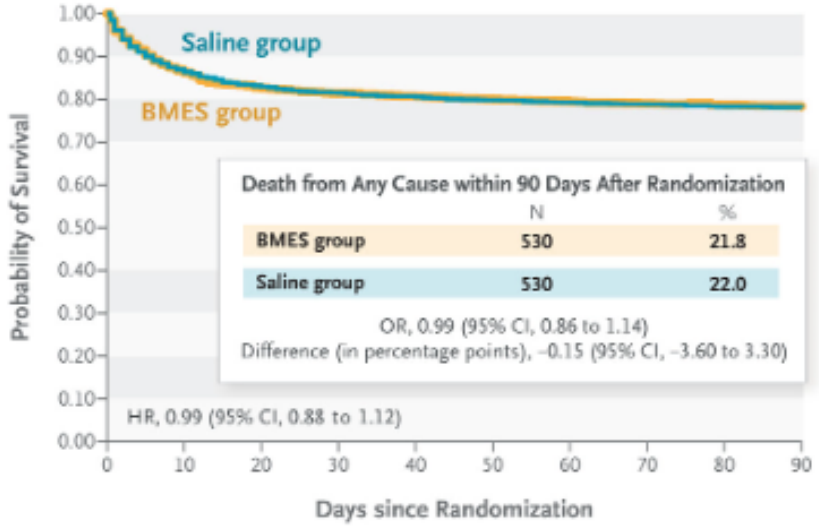
Higher mortality in TBI subgroup
- Balanced: 31%
- Saline: 21%





Zampieri et al. *JAMA 2021*

PLUS Trial



Secondary Outcomes

	BMES	Saline
Maximum creatinine level in the ICU during days 1 to 7, mg/dl Absolute difference, 0.01 (−0.04 to 0.06)	1.76±1.44	1.75±1.43
Maximum increase in creatinine level in the ICU, mg/dl Absolute difference, 0.01 (−0.05 to 0.06)	0.41±1.06	0.41±1.02
Receipt of new renal-replacement therapy, no. (%) OR, 0.98 (0.83 to 1.16) Absolute difference, −0.20 (−2.96 to 2.56) percentage points	306 (12.7)	310 (12.9)

5037 patients; 53 ICUs

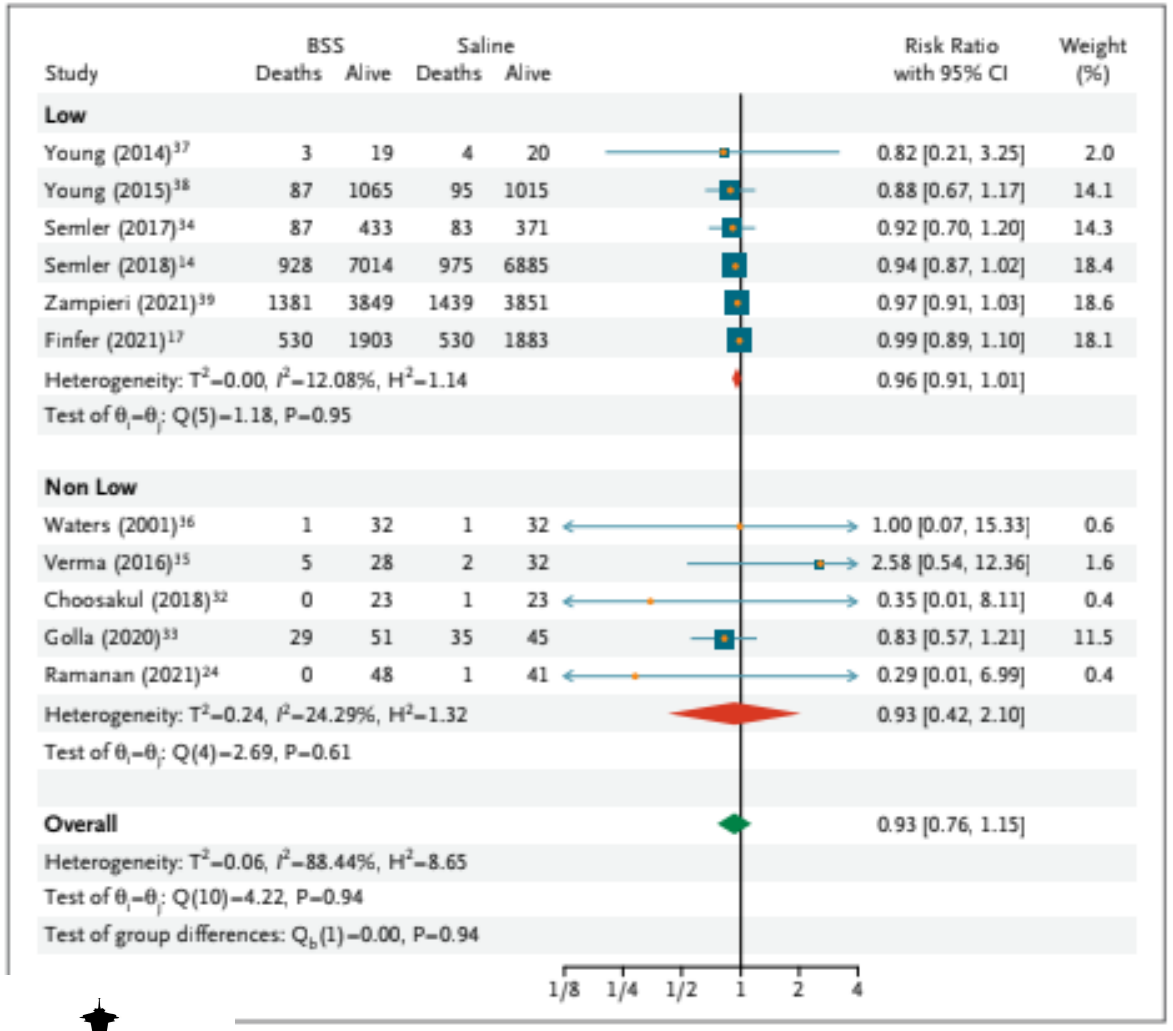
4.1L over first 3 days

Balanced = Plasma-Lyte 148

Pre-randomization fluids
- 1L saline
- 631 ml balanced
- 39% received >500 ml of “other group”

Finfer et al. *NEJM 2021*

Systematic Review & Meta-Analysis

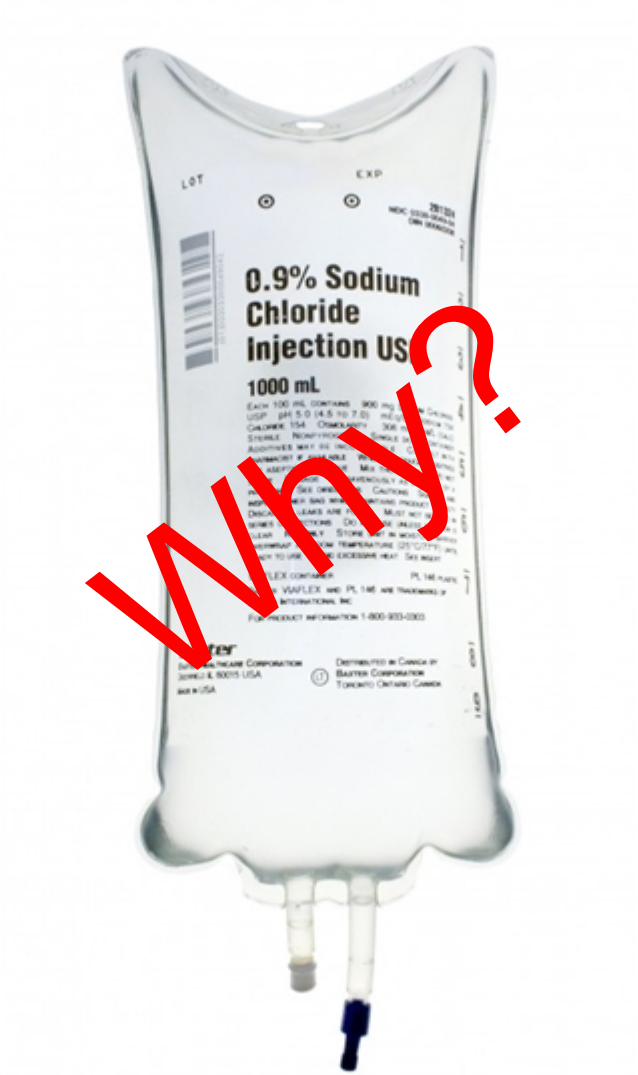


Study	BSS Deaths	BSS Alive	Saline Deaths	Saline Alive	Risk Ratio with 95% CI	Weight (%)
Low						
Young (2014)[37]	3	19	4	20	0.82 [0.21, 3.25]	2.0
Young (2015)[38]	87	1065	95	1015	0.88 [0.67, 1.17]	14.1
Semler (2017)[34]	87	433	83	371	0.92 [0.70, 1.20]	14.3
Semler (2018)[14]	928	7014	975	6885	0.94 [0.87, 1.02]	18.4
Zampieri (2021)[39]	1381	3849	1439	3851	0.97 [0.91, 1.03]	18.6
Finfer (2021)[17]	530	1903	530	1883	0.99 [0.89, 1.10]	18.1
Heterogeneity: T^2=0.00, I^2=12.08%, H^2=1.14					0.96 [0.91, 1.01]	
Test of $\theta_i=\theta_j$: Q(5)=1.18, P=0.95						
Non Low						
Waters (2001)[16]	1	32	1	32	1.00 [0.07, 15.33]	0.6
Verma (2016)[15]	5	28	2	32	2.58 [0.54, 12.36]	1.6
Choosakul (2018)[32]	0	23	1	23	0.35 [0.01, 8.11]	0.4
Golla (2020)[33]	29	51	35	45	0.83 [0.57, 1.21]	11.5
Ramanan (2021)[24]	0	48	1	41	0.29 [0.01, 6.99]	0.4
Heterogeneity: T^2=0.24, I^2=24.29%, H^2=1.32					0.93 [0.42, 2.10]	
Test of $\theta_i=\theta_j$: Q(4)=2.69, P=0.61						
Overall					0.93 [0.76, 1.15]	
Heterogeneity: T^2=0.06, I^2=88.44%, H^2=8.65						
Test of $\theta_i=\theta_j$: Q(10)=4.22, P=0.94						
Test of group differences: $Q_b(1)$=0.00, P=0.94						

"The estimated effect of using balanced crystalloids versus saline in critically ill adults ranges from a 9% relative reduction to a 1% relative increase in the risk of death, with a **high probability that the average effect of using balanced crystalloids is to reduce mortality**."

Hammond et al. *NEJM Evidence* 2022.

A proposal…


0.9% Sodium
Chloride
Injection US
1000 mL
Why?


Plasma-Lyte A
Injection pH 7.4
(Multiple Electrolytes Injection
Type 1 USP)
1000 mL
$$

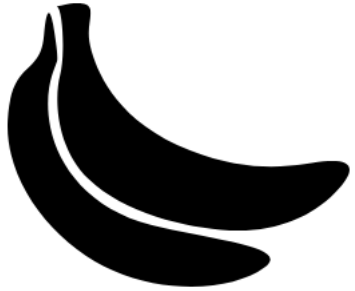

Lactated Ringer's
Injection USP
1000 mL
Winner

Maybe Saline or Plasma-Lyte?

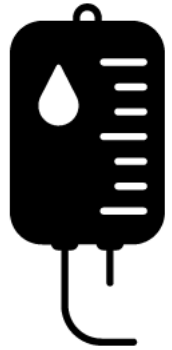
Hypochloremic metabolic alkalosis

Brain Injury

Hyperkalemia



Blood & Medication Compatibility



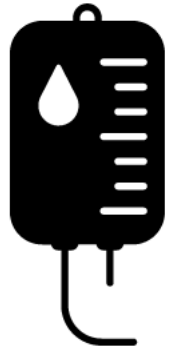
Maybe Saline?

Hypochloremic metabolic alkalosis

Brain Injury

Hyperkalemia

Blood & Medication Compatibility




Fluid Volume
& Timing

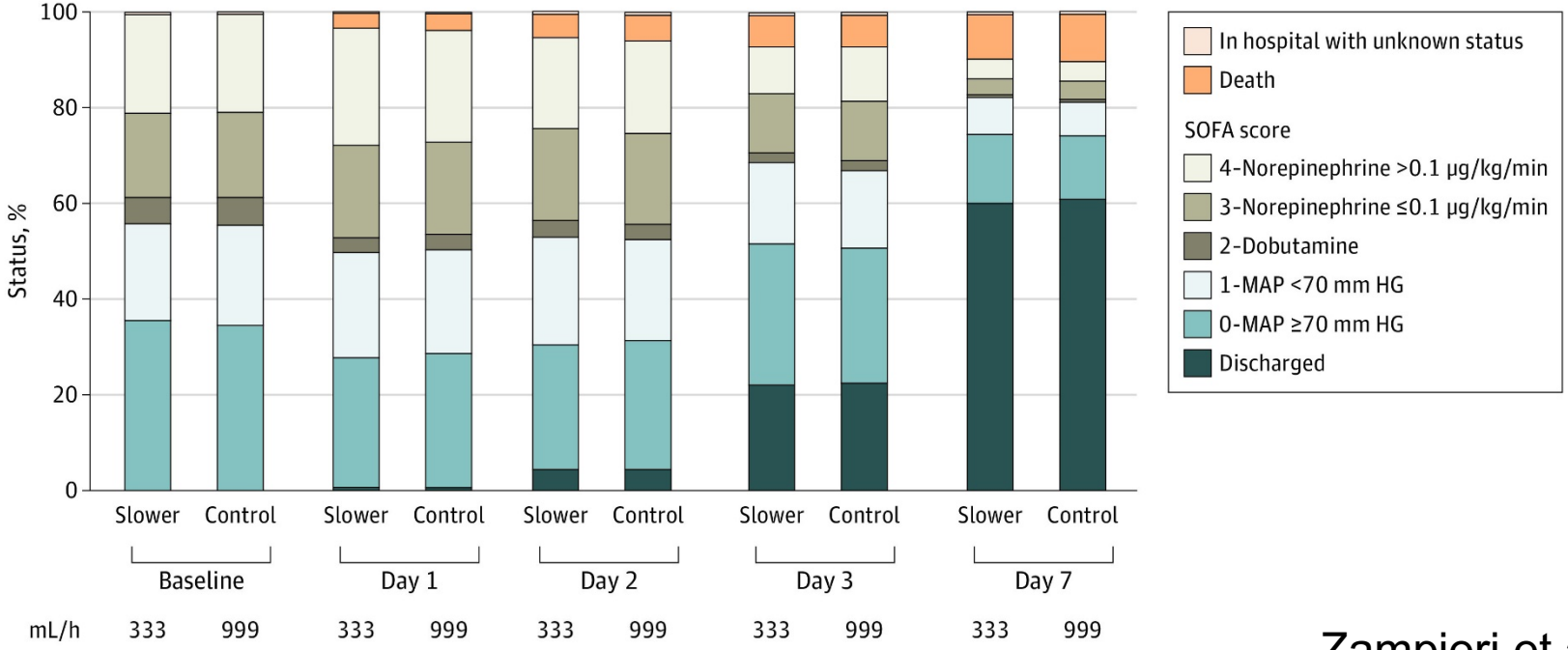
BaSICS Trial – Part 2

11,051 patients; 75 ICUs

4.1L over first 3 days

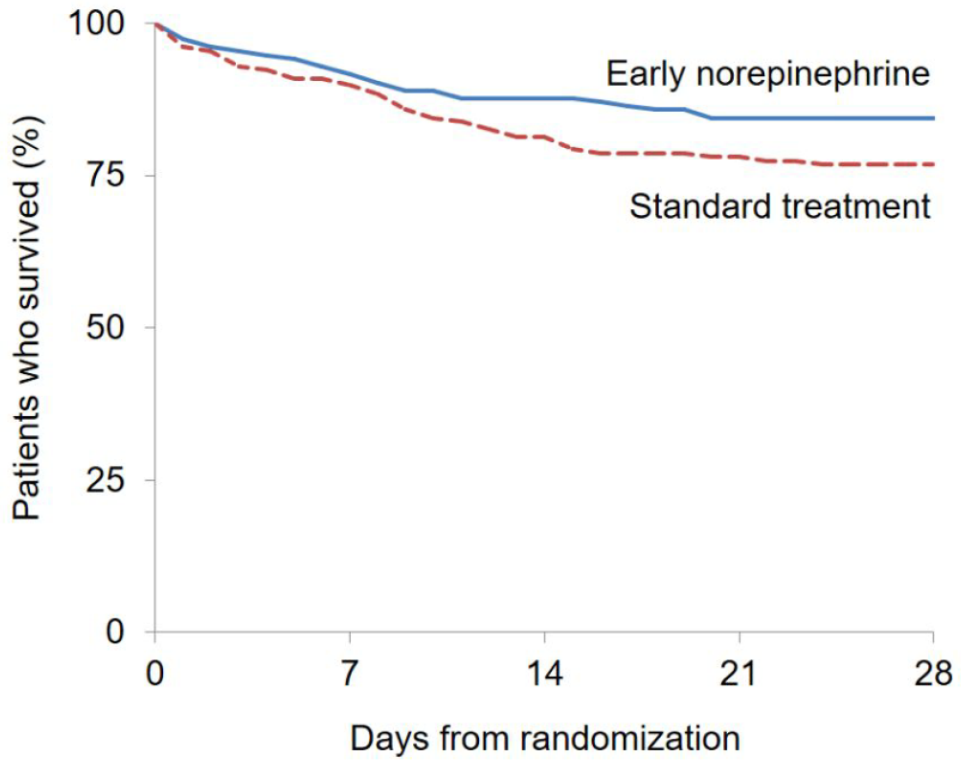
Type	Rate
Balanced	Control (999 ml/hr)
Saline	Slower (333 ml/hr)

No difference in 90-day mortality (27 vs 27%)



Zampieri et al. *JAMA 2021*

CENSER Trial



310 patients with sepsis & hypotension

Early norepinephrine vs standard treatment

Primary outcome: shock control by 6 hours
- Early norepinephrine: 76%
- Standard: 48%

Key Secondary Outcomes
- Less pulmonary edema
- Fewer arrythmias
- No difference in total fluid volume
- No other safety differences (e.g., ischemia)
- Trend toward lower mortality (16 vs 23%)

Permpikul et al. *AJRCCM 2019*

CLOVERS trial

Non-blinded Phase III RCT

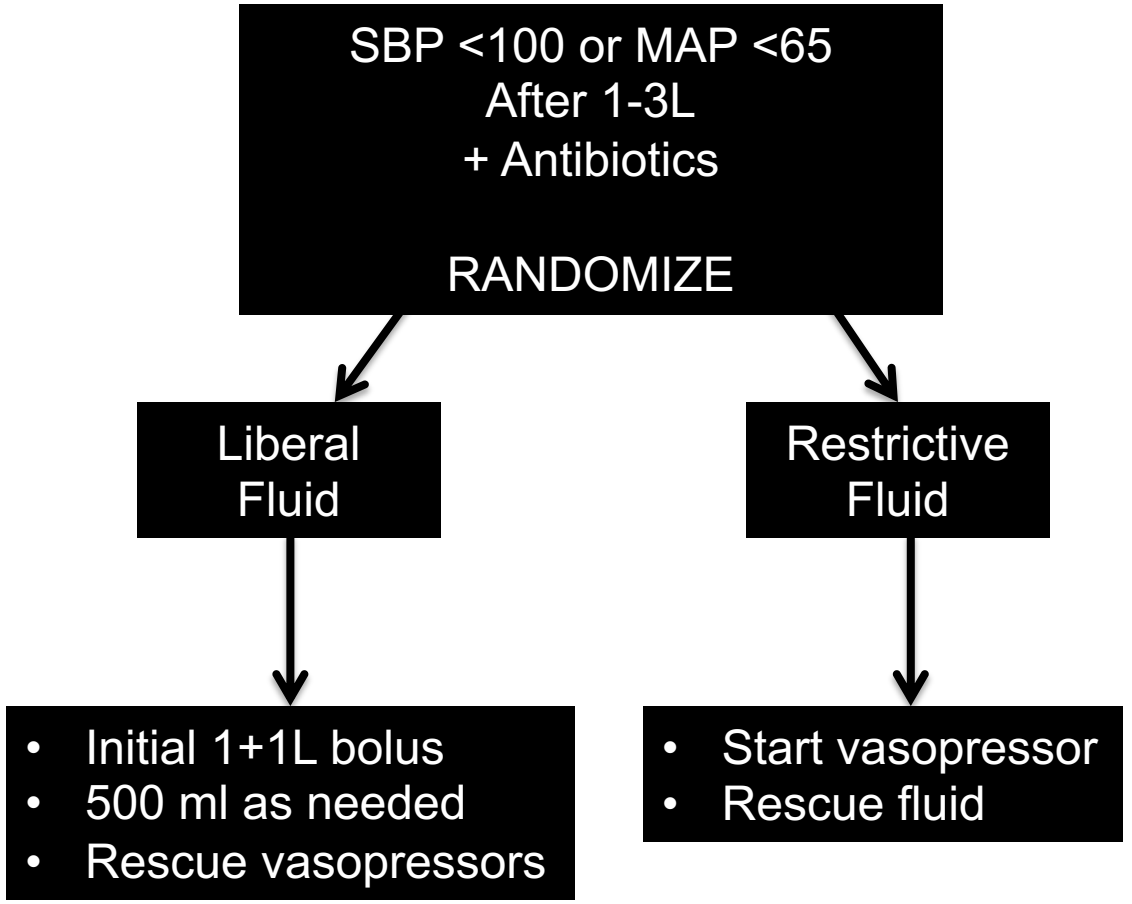
50 US hospitals

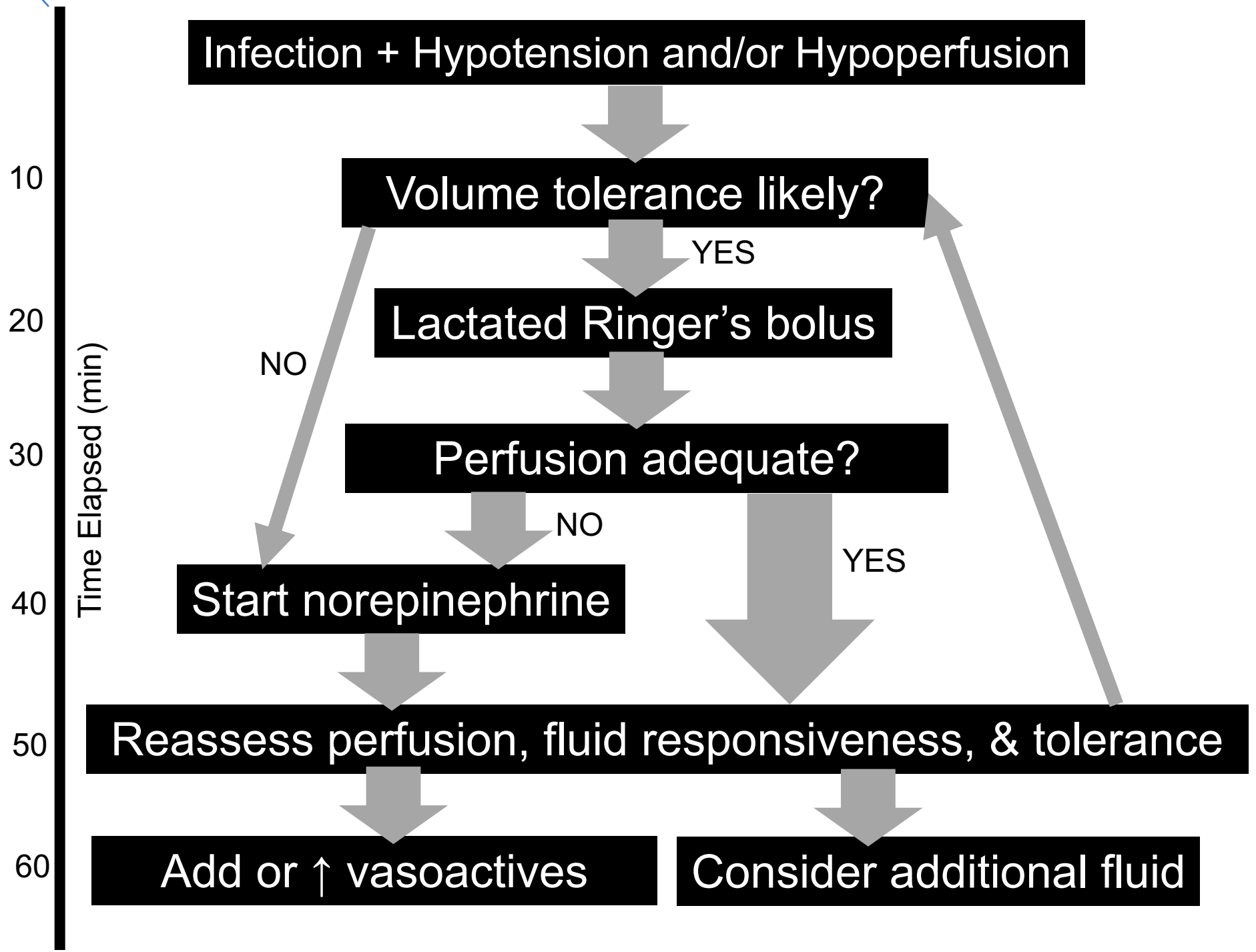
NHLBI PETAL Network

Calculated Sample Size:
2320 patients

Outcome: 90-day mortality

Stopped for futility
1566 patients enrolled




Infection + Hypotension and/or Hypoperfusion
Volume tolerance likely?
YES
NO
Lactated Ringer's bolus
Perfusion adequate?
NO
YES
Start norepinephrine
Reassess perfusion, fluid responsiveness, & tolerance
Add or ↑ vasoactives
Consider additional fluid
Time Elapsed (min)
10
20
30
40
50
60

Take Home

1. **Fluid is a drug.** Prescribe as needed.

2. **Balanced fluids may *modestly* improve outcome.** But why not?

3. **Less is probably more.**

4. **No one-size-fits all approach;** important to have a framework and individualize.

Thank you!

Nick Johnson, MD

nickj45@uw.edu

@NickJohnsonMD