Pragmatic Pediatric Trial of Balanced vs Normal Saline Fluid in Sepsis (PRoMPT BOLUS)

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NIH Pragmatic Trials Collaboratory: Rethinking Clinical Trials

July 10, 2026

ORIGINAL ARTICLE

Balanced Fluid or 0.9% Saline in Children Treated for Septic Shock

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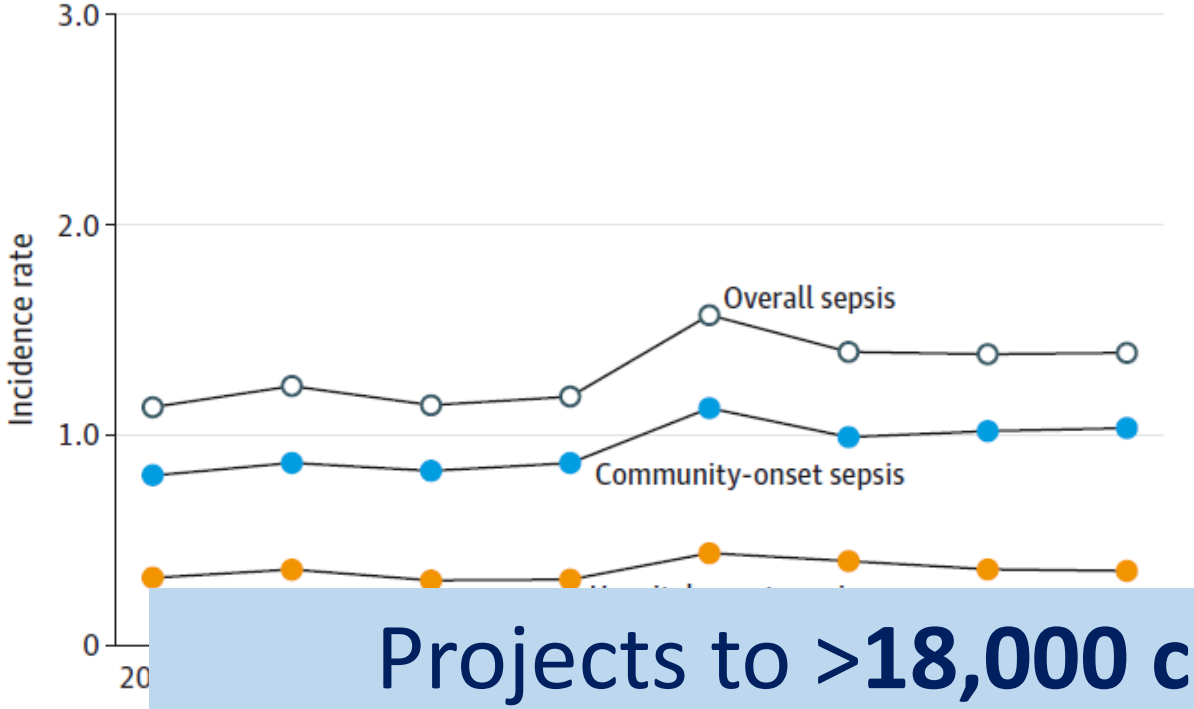
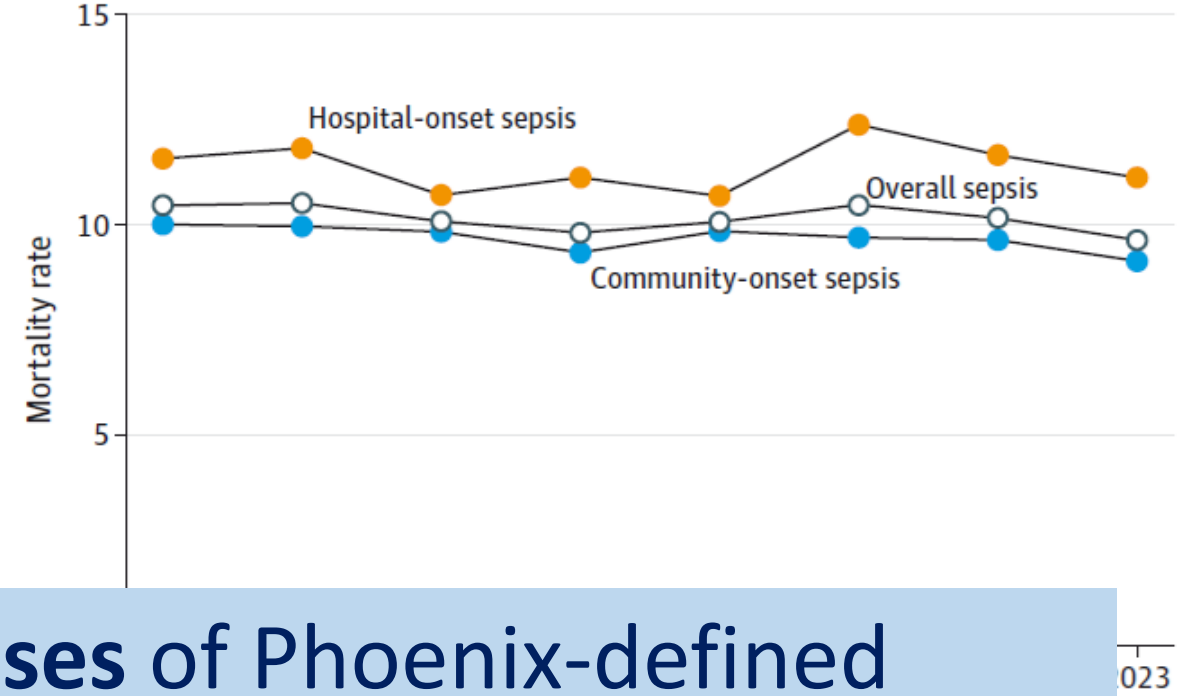
NEJM April 2026

Epidemiology of Pediatric Sepsis – 2024 Phoenix

Incidence



Mortality



Projects to >**18,000 cases** of Phoenix-defined sepsis/septic shock and **1,800 deaths** in US each year

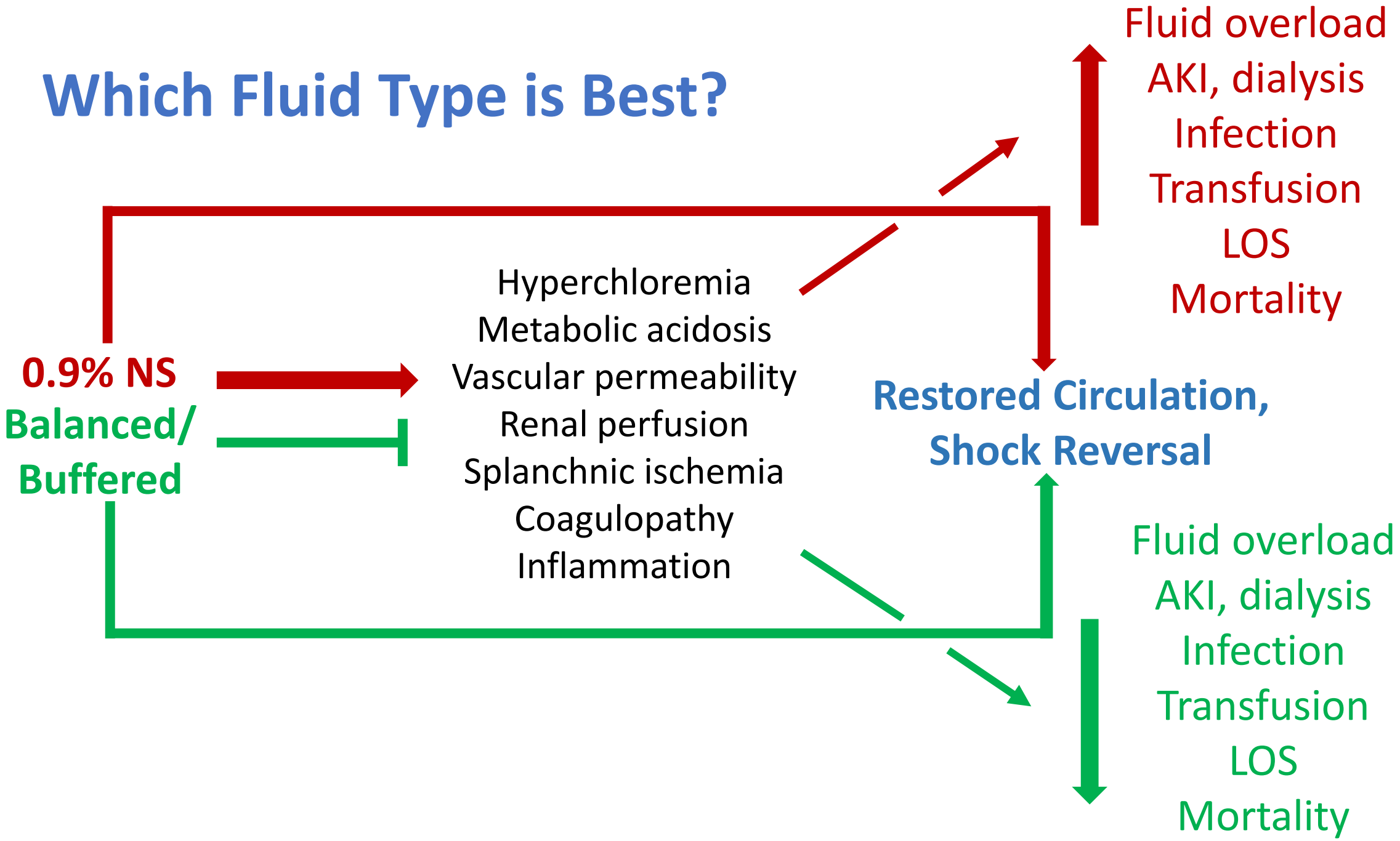
Rhee, Balamuth, Weiss et al *JAMA* 2026

	Blood	0.9% NS	LR (Hartman's)	Plasma-Lyte
Na (mEq/L)	135-145	154	130	140
Cl (mEq/L)	100	154	109	98
K (mEq/L)	3.5-5	0	4	5
Ca (mEq/L)	4.3-5.3	0	2.7	0
Buffer	Multiple	None	Lactate	Acet/Gluc
pH	7.4	5	6.5	7.4
SID (rel to blood)	24	0	28	49
Osmolality	290	308	273	294
Cost (per 500 mL)		$1	$1-2	$3-5

SID = Strong Ion Difference

Bartels et al, *Crit Care* 2013; Yunos et al, *JAMA* 2012

Which Fluid Type is Best?



ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

	SALT-ED	SMART
N	**13,347**	**15,802**
MAKE30	0.82 (0.70, 0.95)	0.90 (0.82, 0.99)
Hospital death	0.88 (0.66, 1.16)	0.90 (0.80, 1.01)

Data are adjusted OR

MAKE30: Major adverse kidney events in 30 days

NEJM 2018

ORIGINAL ARTICLE

A Crossover Trial of Hospital-Wide Lactated Ringer's Solution versus Normal Saline

N = 43,626 patients in 7 academic & community hospitals in Ontario, Canada

Outcome	Lactated Ringer's Solution (N=7)	Normal Saline (N=7)	Adjusted Mean Difference (95% CI)†	Adjusted Relative Difference (95% CI)
Primary outcome				
Composite of death or readmission within 90 days after index admission (%)	20.3±3.5	21.4±3.3	−0.53 (−1.85 to 0.79)‡	0.97 (0.90 to 1.05)
Secondary outcomes				
Death within 90 days after index admission (%)	6.9±1.2	7.6±1.7	−0.26 (−0.95 to 0.43)	0.97 (0.89 to 1.07)
Readmission to hospital within 90 days after index admission (%)	15.1±2.9	15.4±2.1	−0.06 (−1.78 to 1.67)	0.99 (0.87 to 1.11)
Emergency department visit within 90 days after index admission (%)§	21.2±3.1	21.0±2.3	0.28 (−2.51 to 3.06)	1.01 (0.88 to 1.15)
Initiation of dialysis within 90 days after index admission (%)	0.5±0.3	0.6±0.5	−0.12 (−0.34 to 0.11)	0.99 (0.56 to 1.77)
Hospital length of stay (hr)	164.7±34.7	172.3±34.2	−0.002 (−0.006 to 0.002)	NA¶
Discharge to a facility other than home (%)	15.4±4.8	16.2±4.6	−0.49 (−1.59 to 0.62)	0.96 (0.90 to 1.03)

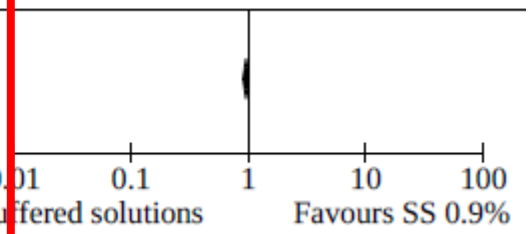
McIntyre et al *NEJM* 2025

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

Mortality

Study or Subgroup	log[OR]	SE	Buffered solutions Total	SS 0.9% Total	Weight	Odds Ratio IV, Random, 95% CI
Total (Wald[a])			**18287**	**18165**	**100.0%**	**0.95 [0.90 , 1.01]**

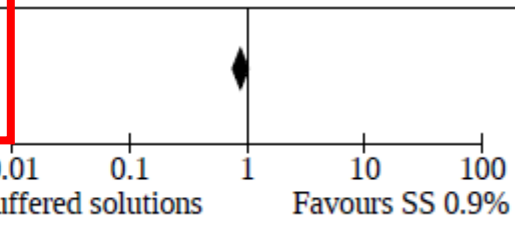
Test for overall effect: Z = 1.68 (P = 0.09)



Acute Kidney Injury

Study or Subgroup	log[OR]	SE	Buffered solutions Total	SS 0.9% Total	Weight	Odds Ratio IV, Random, 95% CI
Total (HKSJ[a])			**15575**	**15257**	**100.0%**	**0.87 [0.75 , 1.02]**

Test for overall effect: T = 1.85, df = 16 (P = 0.08)



Moya et al *Cochrane Reviews* 2026

PRoMPT BOLUS Study Design Overview

- **Design:** Large pragmatic randomized clinical trial
- **Population:** Suspected septic shock, 2 mos to <18 yrs
- **Setting:** ED (with extension to ward, ICU)
- **Enrollment:** Exception from informed consent
- **Intervention:** LR (or PlasmaLyte) versus 0.9% saline
- **Allocation:** Randomized 1:1, open-label
- **1° outcome:** Major adverse kidney events (MAKE30)
- **Sample size:** 8,800
- **Duration:** 5 years

	Explanatory RCT	Pragmatic RCT	PRoMPT BOLUS
Objective	Efficacy or Mechanism	Effectiveness	Most effective fluid type
Study population	Restrictive, homogeneous	Heterogeneous	Children treated for septic shock
Intervention	Inflexible, strictly enforced	Usual practice #1	Balanced fluid
Comparison	Inflexible, +/- placebo	Usual practice #2	0.9% saline
Data collection	Extensive, labor-intensive	Targeted, limited	Targeted, limited
Protocol adherence	Closely monitored	Unobtrusive or none	1. Enroll ≥80% eligible 2. Randomized fluid for ≥75% of total crystalloids
Outcome(s)	Direct consequence of intervention, spec training	Objective, clinically-meaningful, easily measured	Routine clinical data in EHR
Analysis	ITT + Per-protocol ("works under ideal conditions")	ITT ("works under usual conditions")	ITT + Per-protocol
Generalizability	Variable (often low)	High	High
"Foot soldiers"	Dedicated research team	Front-line clinicians	Front-line clinicians
Costs	Relatively high	Relatively low	Relatively low

Pragmatic Eligibility Criteria

Inclusion Criteria

- Age >2 mos to <18 years
- Suspected septic shock
  - Parenteral antibiotics
  - Blood culture
  - Fluid bolus *for abnormal perfusion or hypotension*

  OR

  - Initiate sepsis pathway
  - Expect >1 fluid bolus

Exclusion Criteria

- >40 mL/kg fluid (or unverified volume)
- Clinician judgment not safe
  - *Suspected* brain herniation
  - *Known* hyperkalemia, hypercalcemia
  - *Known* hepatic, renal failure
  - *Known* metabolic or mitochondrial disease
- *Known* pregnancy, prisoner, fluid allergy
- *Known* “opt-out”

Pragmatic Bedside Enrollment

- ED clinicians:
  - Determined eligibility
  - *Brief* verbal opt-out discussion
  - Randomized (serially numbered opaque envelopes)
    - *Randomization 1:1, permuted blocks, stratified by site
  - Began study fluid
  - Handed-off to inpatient team

Pragmatic Intervention

- Control group: 0.9% saline = “usual practice”
- Intervention: Balanced Fluids (LR, Pedialyte, Hartmann’s)

- Study fluid (Balanced or 0.9% saline) through 11:59 pm next study day
- Recommend study fluid for bolus + maintenance
  - Isotonic fluids recommended for critically ill children*
  - OK to add dextrose, electrolytes
  - Alternative fluid as clinically indicated

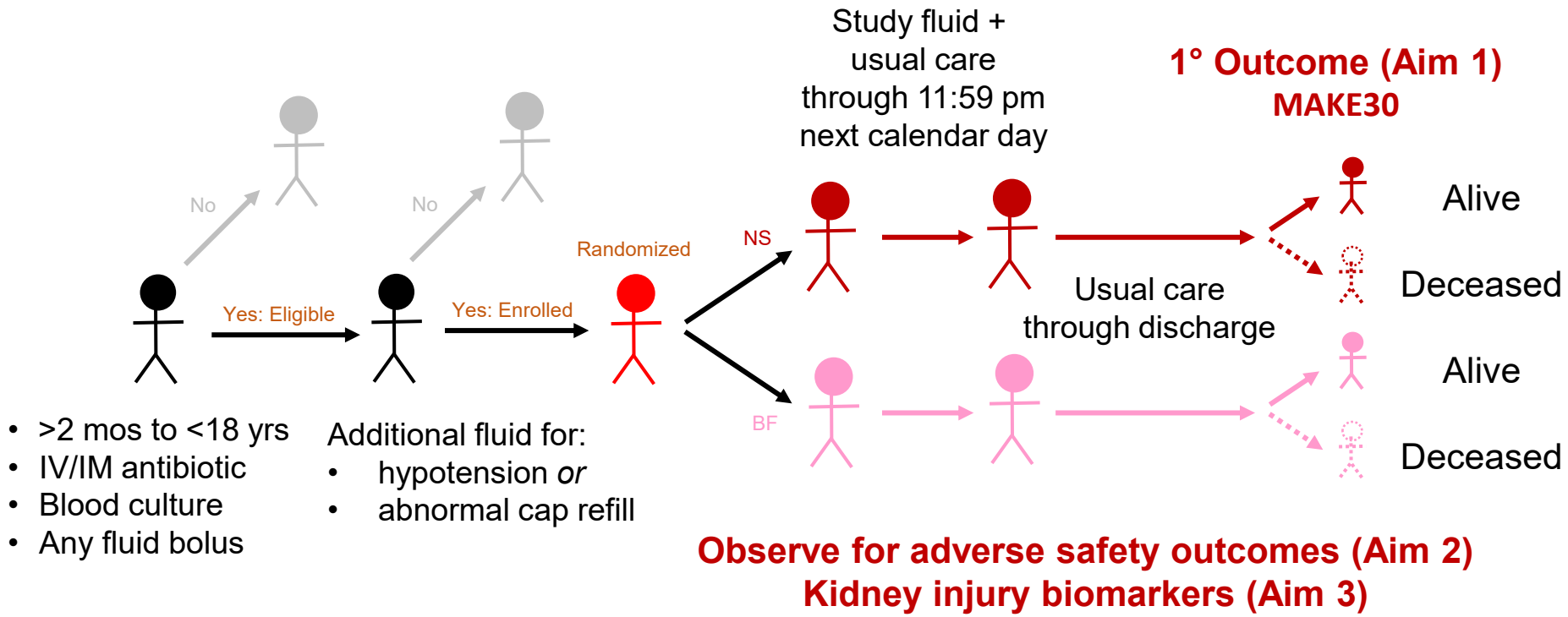
- Study fluid <u>not blinded</u>

*Feld et al *Pediatrics* 2018

Exception From Informed Consent (EFIC)

1. Subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety, effectiveness of therapy
2. Obtaining prospective informed consent not feasible
3. Subjects may benefit from the research
4. Research could not be carried out without an EFIC

Study Design Overview



Pragmatic Pediatric Trial of Balanced Versus Normal Saline Fluid in Sepsis: The PRoMPT BOLUS Randomized Controlled Trial Pilot Feasibility Study

Fran Balamuth, MD, PhD, MSCE[1,2], Marlena Kittick, MPH[1], Peter McBride[1], Ashley L. Woodford[1], Nicole Vestal[1], Mary Kate Abbadessa, MSN, RN[1], T. Charles Casper, PhD[3], Melissa Metheney, RN[3], Katherine Smith, MPH, BSN, RN[4], Natalie J. Atkin[4], Jill M. Baren, MD[1,5], J. Michael Dean, MD[3], Nathan Kuppermann, MD, MPH[6], and Scott L. Weiss, MD, MSCE[2,4]

Aim	Outcome
Feasibility	**85%** of eligible patients enrolled
Acceptability of EFIC	**98%** completed study
Protocol Adherence	**92%** NS group, **83%** BF group

EFIC, exception from informed consent
NS, 0.9% 'normal' saline; BF, balanced fluid

Balamuth, Weiss et al *Acad Emerg Med* 2019

Primary Endpoint: MAKE30

- Major adverse kidney events within 30 days
- Composite endpoint
  1. Death
  2. New renal replacement therapy
  3. Persistent kidney dysfunction*

  *Last creatinine before discharge or 30 days is >200% of baseline (baseline measured or imputed)

- Associated with CKD and long-term morbidity/mortality
- Recommended by NIH as a patient-centered outcome for trials

Weiss, Balamuth et al *CJASN* 2019

MAKE 30 in Pediatric Sepsis

1,685 children primarily treated in a PHIS+ hospital (84% ED)

Outcome	PHIS+
MAKE 30	9.6% (95% CI 8.2, 11.1%)
Mortality	4.5%
Renal replacement therapy	1.7%
Persistent kidney dysfunction	5.8%

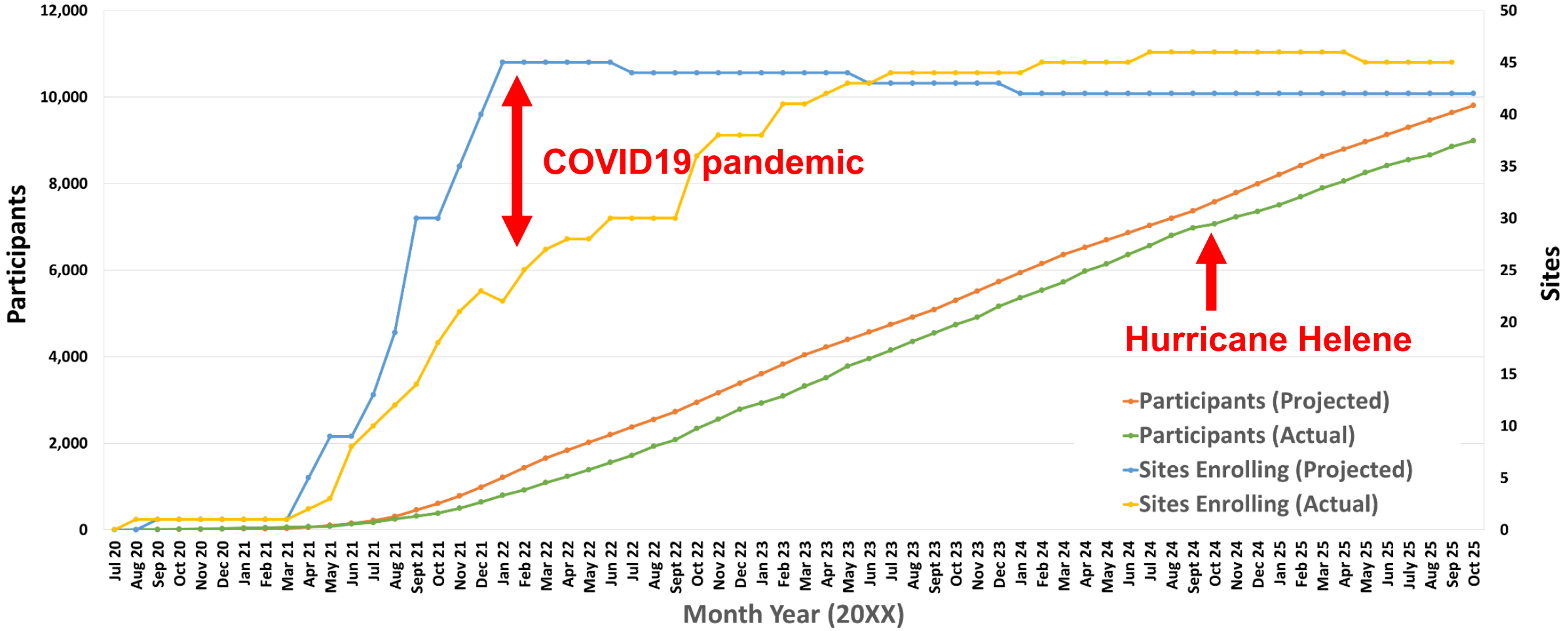
MAKE30 associated with hospital mortality, costs, and CKD

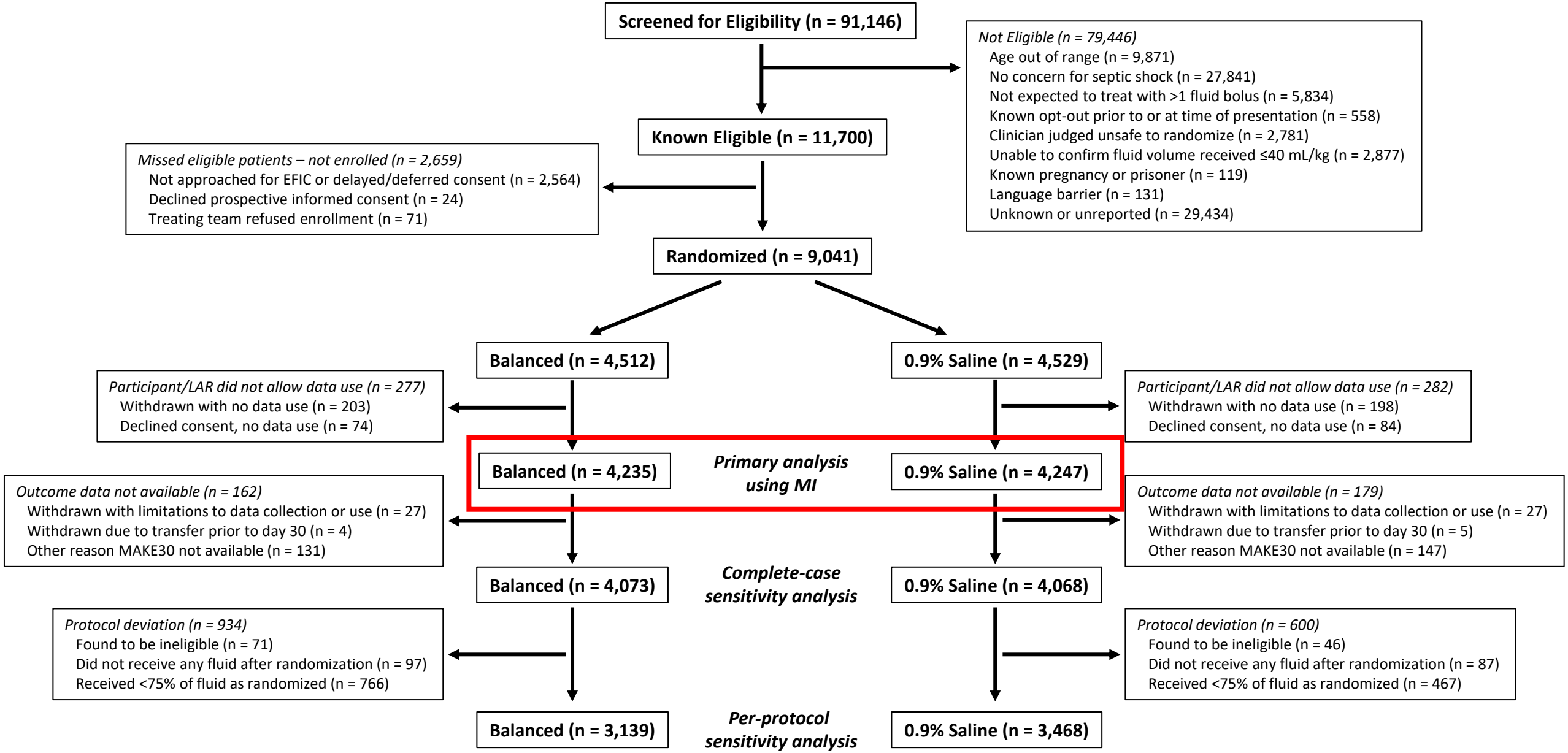
Weiss, Balamuth, Fitzgerald et al *CJASN* 2019

Secondary Endpoints

Effectiveness	Safety	Biological
MAKE30 components	Electrolyte abnormalities	NGAL (urine)
Hospital-free days	Hyperlactatemia	KIM-1 (urine)
Mortality (discharge)	Catheter thrombosis	L-FBP (urine)
Mortality (90 days)	Thromboembolism	IL-18 (urine)
	Brain herniation	Cystatin C (plasma)

Study Enrollment





Balamuth, Weiss et al *NEJM* 2026

Most Enrolled via EFIC or Delayed Consent

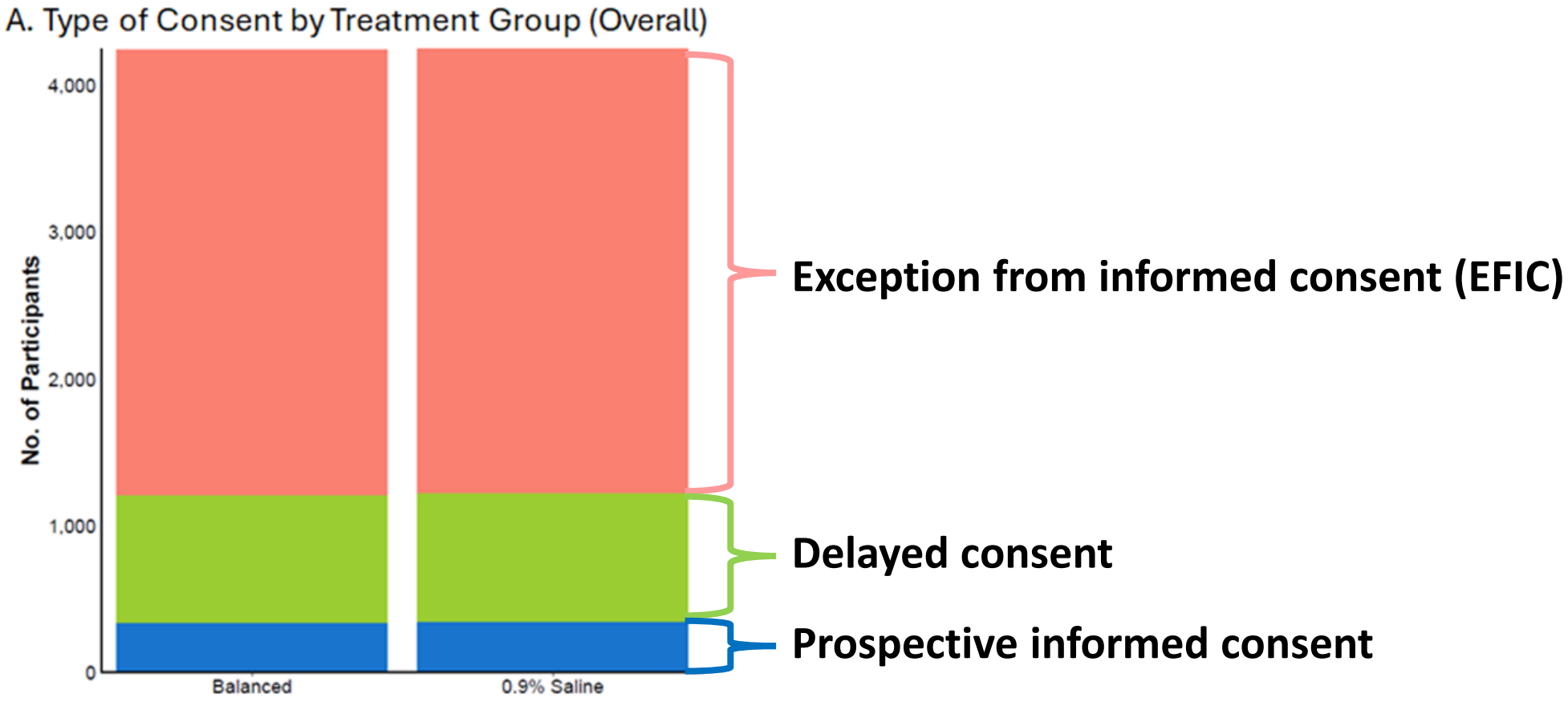


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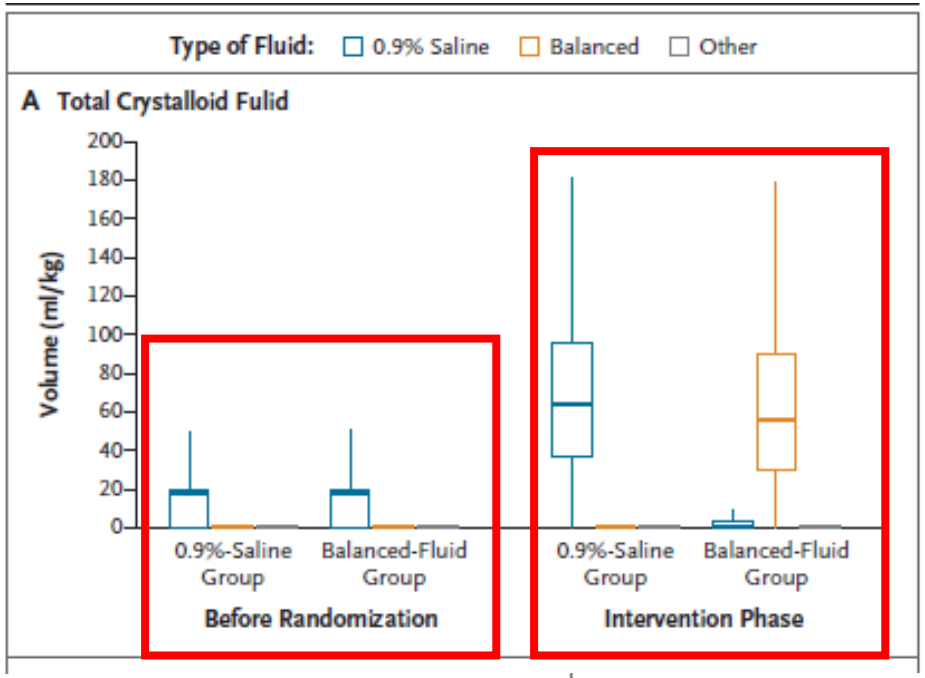
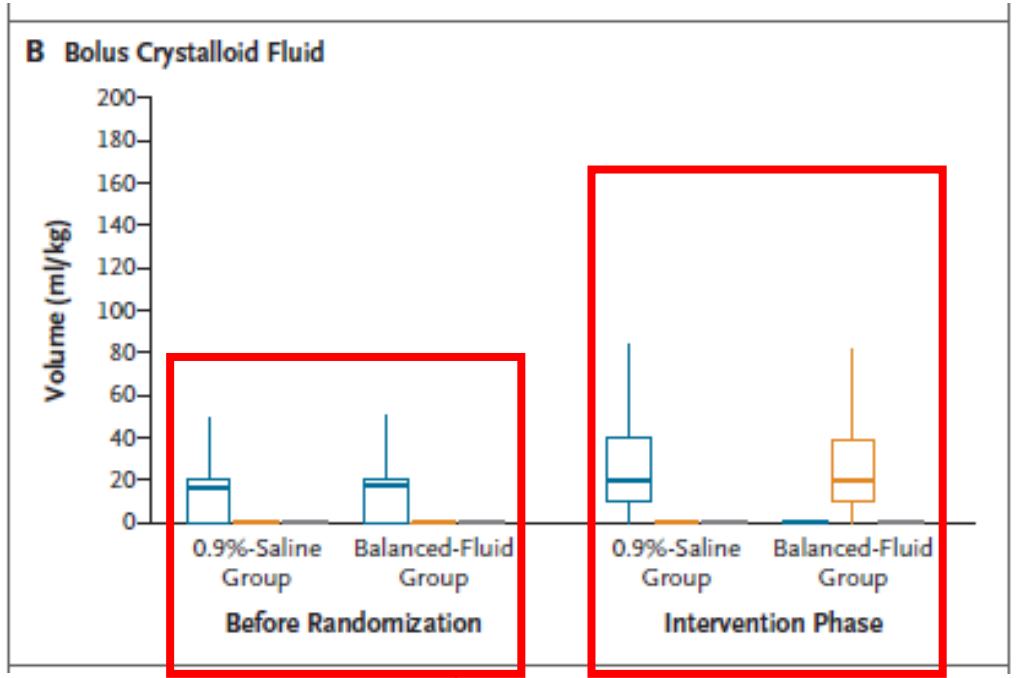
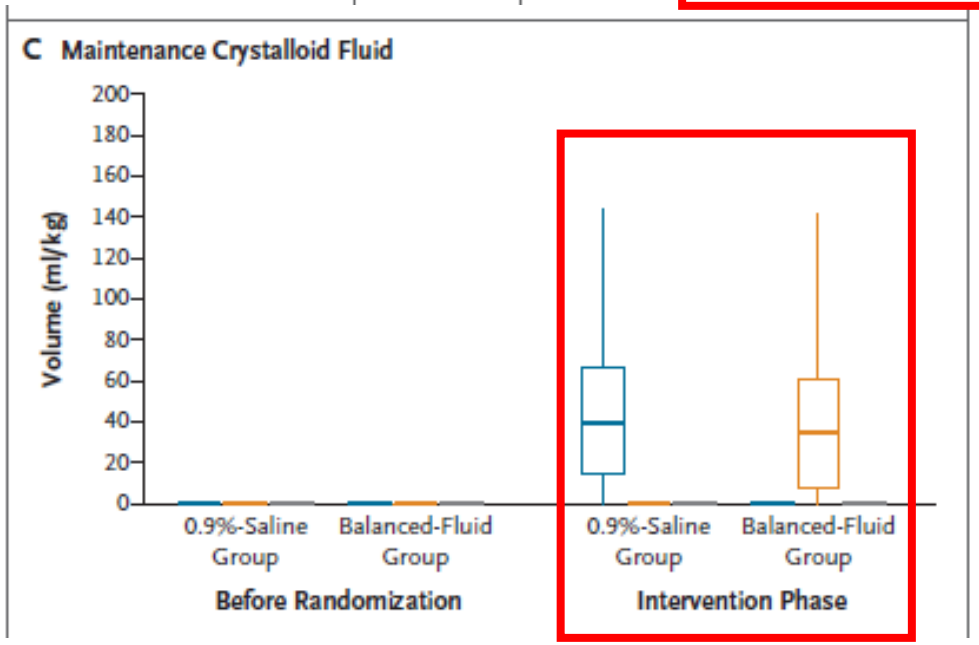
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Balanced Fluid (N=4235)	0.9% Saline (N=4247)
Median age (IQR) — yr†	6.8 (2.8–12.8)	6.8 (2.8–12.8)
Male sex — no./total no. (%)	2166/4232 (51.2)	2136/4242 (50.4)
Coexisting conditions — no./total no. (%)		
Hematogenous or solid-tumor cancer	603/4224 (14.3)	613/4236 (14.5)
Bone marrow or solid-organ transplant	165/4224 (3.9)	158/4236 (3.7)
Cardiomyopathy or heart failure	43/4224 (1.0)	47/4236 (1.1)
Pulmonary hypertension	28/4224 (0.7)	30/4236 (0.7)
Kidney disease	193/4224 (4.6)	175/4236 (4.1)
Neurologic dysfunction causing severe developmental delay	1182/4224 (28.0)	1182/4236 (27.9)
Sickle cell disease	61/4224 (1.4)	59/4236 (1.4)
Chronic ventilator dependence	247/4224 (5.8)	219/4236 (5.2)
Indwelling central catheter	745/4224 (17.6)	742/4236 (17.5)
Median time from emergency department arrival to first antibiotic administration (IQR) — min‡	94 (50–183)	90 (48–183)
Median time from emergency department arrival to trial enrollment (IQR) — min§	103 (50–191)	101 (49–188)
Median volume of crystalloid fluid received before enrollment (IQR) — ml/kg		
0.9% Saline	18 (0–20)	17 (0–20)
Balanced fluid	0 (0–0)	0 (0–0)
Median initial blood lactate level (IQR) — mmol/liter¶	1.9 (1.3–3.0)	1.9 (1.3–3.0)
Median baseline serum creatinine level (IQR) — mg/dl‖	0.30 (0.25–0.50)	0.30 (0.25–0.47)
Acute kidney injury stage at enrollment — no. (%)**		
Stage 1	560 (13.2)	612 (14.4)
Stage 2	201 (4.7)	214 (5.0)
Stage 3	204 (4.8)	228 (5.4)







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Concurrent Sepsis Therapies

Therapy	Balanced Fluid	0.9% Saline
	(n =4,235)	(n = 4,247)
Ceftriaxone – n (%)[a]	2,593 (61)	2,654 (63)
Vasoactive medication(s) – n (%)[b,c]	599 (14)	608 (14)
Corticosteroids – n (%)[b]	956 (23)	923 (22)
Bicarbonate or other buffer – n (%)[b]	194 (4.6)	249 (5.9)
Invasive mechanical ventilation – n (%)[b,d]	410 (9.7)	412 (9.7)
Extracorporeal membrane oxygenation – n (%)[b]	26 (<1)	20 (<1)

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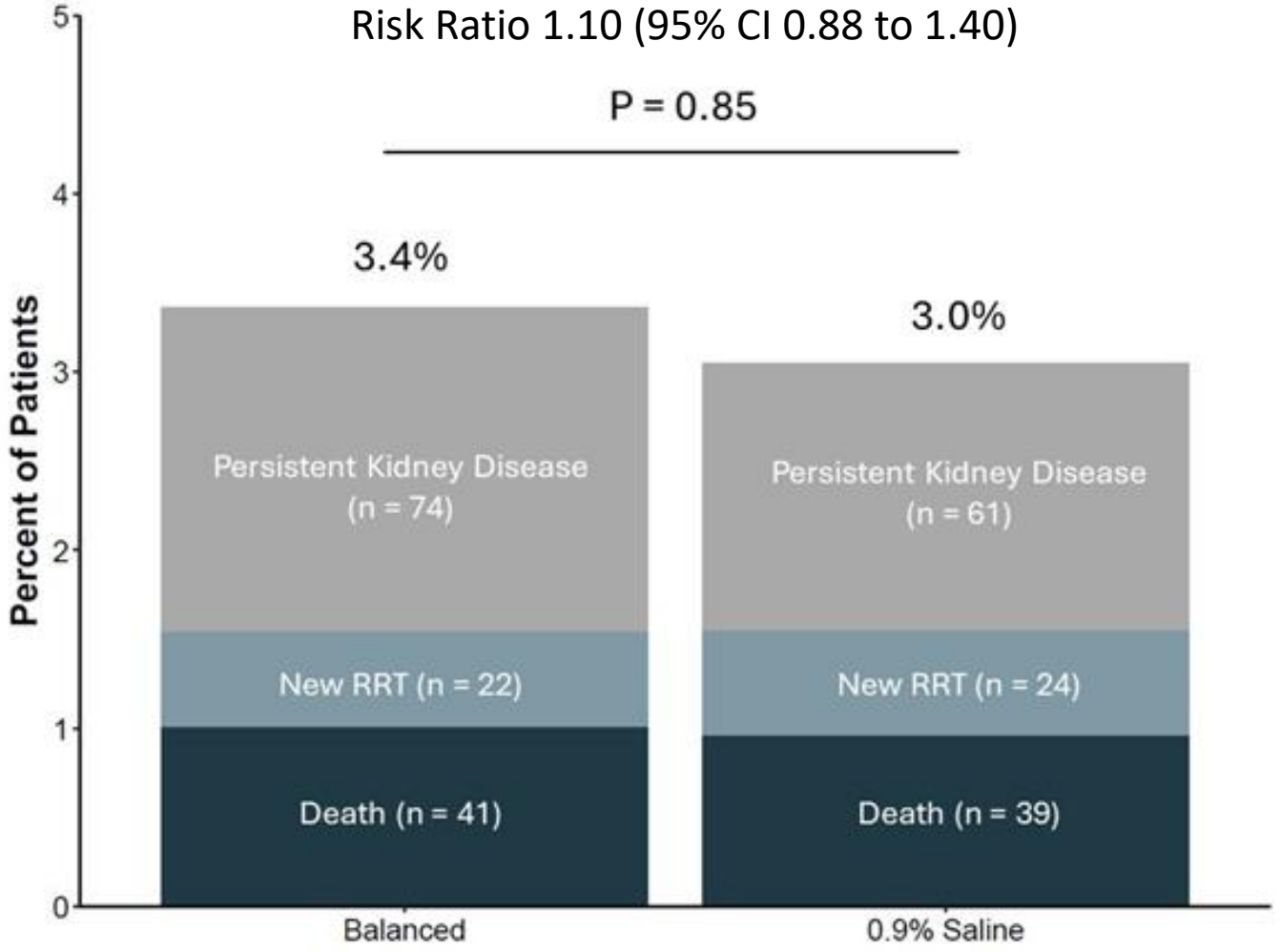
Primary Outcome: MAKE30



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Effectiveness Outcomes

Table 2. Primary, Secondary, and Safety Outcomes.

Outcome*	Balanced Fluid	0.9% Saline	Effect Measure (95% CI)‡	P Value§
Primary outcome				
Major adverse kidney event within 30 days — no./total no. (%)¶	137/4073 (3.4)	124/4068 (3.0)	1.10 (0.88 to 1.40)	0.85
Secondary effectiveness outcomes				
Death within 30 days — no./total no. (%)	41/4214 (1.0)	39/4226 (0.9)	1.07 (0.70 to 1.64)	
New renal-replacement therapy — no./total no. (%)	26/4214 (0.6)	31/4226 (0.7)	0.84 (0.50 to 1.42)	
Persistent kidney dysfunction at hospital discharge — no./total no. (%)	93/4085 (2.3)	78/4079 (1.9)	1.15 (0.88 to 1.49)	
Death before hospital discharge — no. /total no. (%)	48/4216 (1.1)	47/4230 (1.1)	1.02 (0.69 to 1.51)	
Death within 90 days — no./total no. (%)‖	90/3857 (2.3)	83/3867 (2.1)	1.07 (0.80 to 1.42)	
Median length of hospital stay (IQR) — days**	5.0 (3.0 to 9.0)	5.0 (3.0 to 9.0)	0 (0 to 0)	
Median no. of hospital-free days during 28 days (IQR)††	23 (19 to 25)	23 (19 to 25)	0 (0 to 0)	

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Safety Outcomes

Table 2. Primary, Secondary, and Safety Outcomes.

Outcome*	Balanced Fluid	0.9% Saline	Effect Measure (95% CI)‡	P Value§
Safety outcomes — no./total no. (%)‡‡				
Thrombosis	55/4216 (1.3)	55/4230 (1.3)	1.00 (0.69 to 1.45)	0.91
Cerebral edema	18/4216 (0.4)	17/4230 (0.4)	1.09 (0.55 to 2.13)	0.57
Sodium >155 mmol/liter	52/2830 (1.8)	89/2882 (3.1)	0.60 (0.43 to 0.84)§§	0.003
Sodium <128 mmol/liter	2/2830 (0.1)	0/2882 (0)	—	—
Chloride >110 mmol/liter	868/2765 (31.4)	1383/2823 (49.0)	0.64 (0.60 to 0.69)§§	<0.001
Potassium >6 mmol/liter	63/2798 (2.3)	74/2853 (2.6)	0.87 (0.62 to 1.20)§§	0.39
Total calcium level >12 mg/dl or ionized calcium level >1.35 mmol/liter	127/926 (13.7)	140/1005 (13.9)	0.95 (0.76 to 1.18)§§	0.62
Lactate level >4 mmol/liter	260/1314 (19.8)	228/1363 (16.7)	1.18 (1.01 to 1.39)§§	0.04

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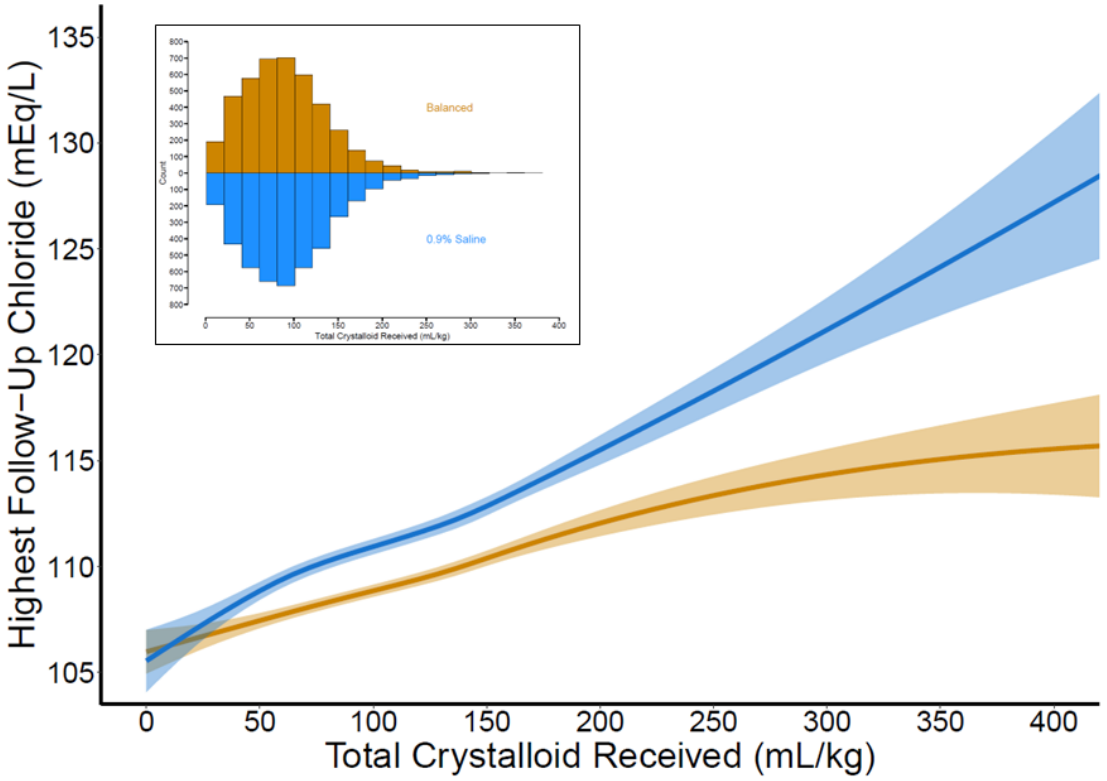
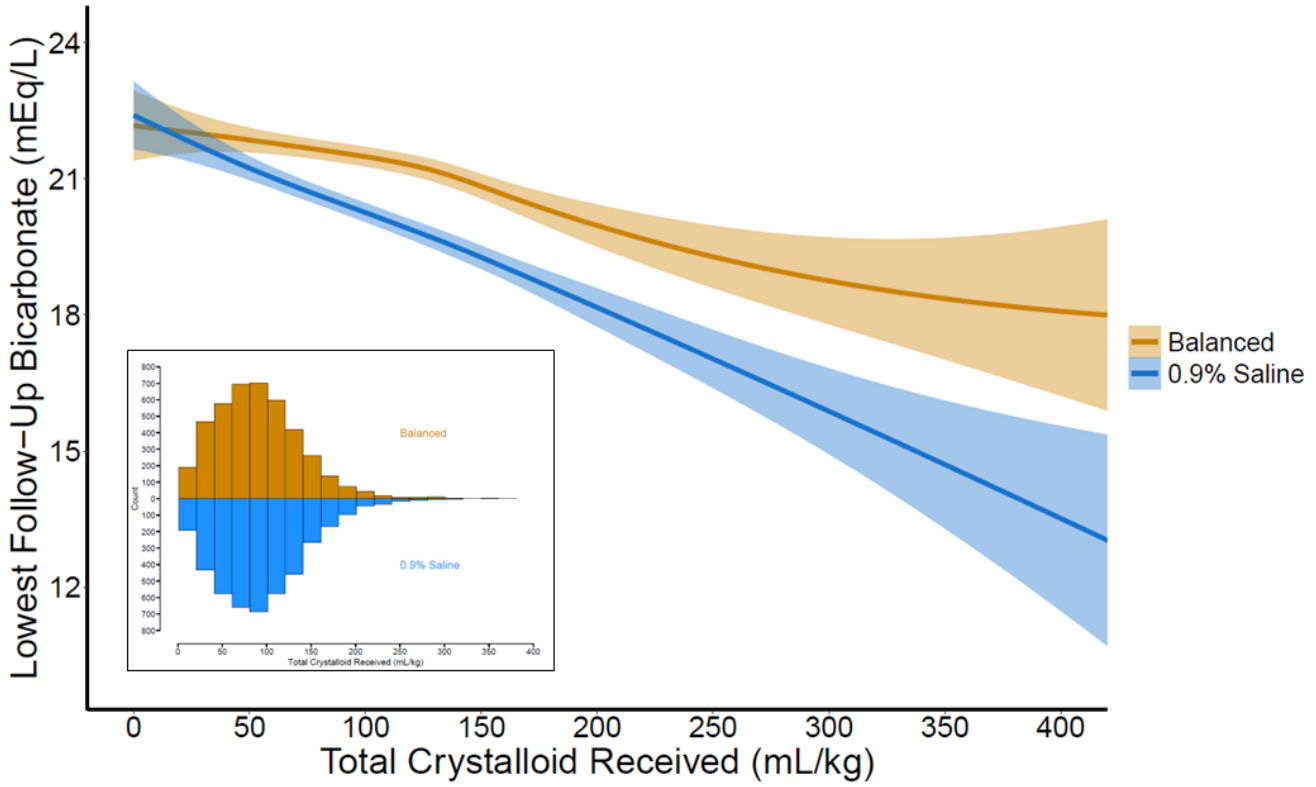
Effect of Fluid Volume on Blood Electrolytes

Chloride



Bicarbonate



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Country

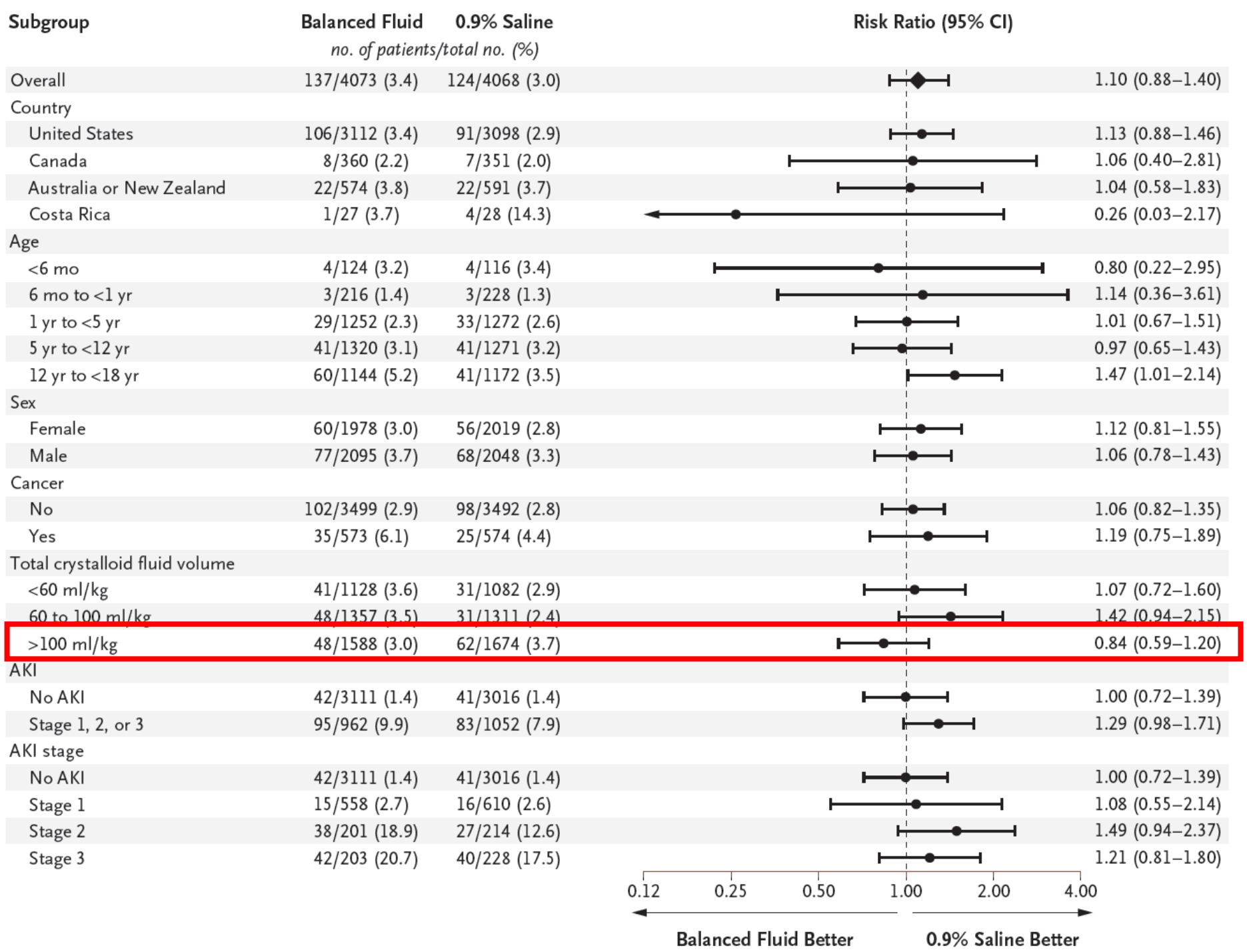
Age

Sex

Cancer

Fluid volume

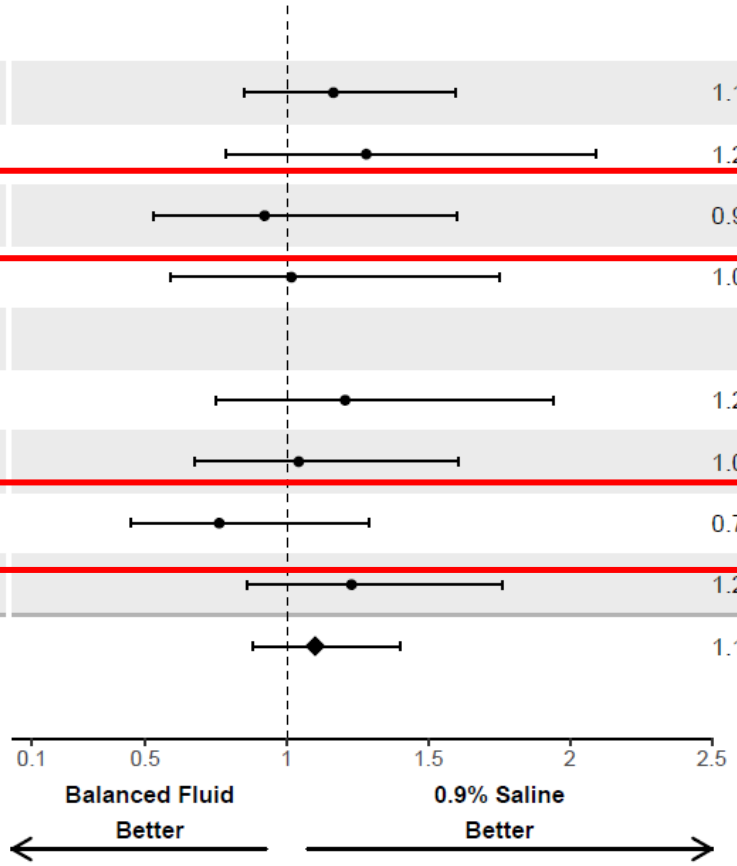
AKI at presentation



Subgroup	Balanced Fluid	0.9% Saline	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
Overall	137/4073 (3.4)	124/4068 (3.0)	1.10 (0.88–1.40)
Country			
United States	106/3112 (3.4)	91/3098 (2.9)	1.13 (0.88–1.46)
Canada	8/360 (2.2)	7/351 (2.0)	1.06 (0.40–2.81)
Australia or New Zealand	22/574 (3.8)	22/591 (3.7)	1.04 (0.58–1.83)
Costa Rica	1/27 (3.7)	4/28 (14.3)	0.26 (0.03–2.17)
Age			
<6 mo	4/124 (3.2)	4/116 (3.4)	0.80 (0.22–2.95)
6 mo to <1 yr	3/216 (1.4)	3/228 (1.3)	1.14 (0.36–3.61)
1 yr to <5 yr	29/1252 (2.3)	33/1272 (2.6)	1.01 (0.67–1.51)
5 yr to <12 yr	41/1320 (3.1)	41/1271 (3.2)	0.97 (0.65–1.43)
12 yr to <18 yr	60/1144 (5.2)	41/1172 (3.5)	1.47 (1.01–2.14)
Sex			
Female	60/1978 (3.0)	56/2019 (2.8)	1.12 (0.81–1.55)
Male	77/2095 (3.7)	68/2048 (3.3)	1.06 (0.78–1.43)
Cancer			
No	102/3499 (2.9)	98/3492 (2.8)	1.06 (0.82–1.35)
Yes	35/573 (6.1)	25/574 (4.4)	1.19 (0.75–1.89)
Total crystalloid fluid volume			
<60 ml/kg	41/1128 (3.6)	31/1082 (2.9)	1.07 (0.72–1.60)
60 to 100 ml/kg	48/1357 (3.5)	31/1311 (2.4)	1.42 (0.94–2.15)
>100 ml/kg	48/1588 (3.0)	62/1674 (3.7)	0.84 (0.59–1.20)
AKI			
No AKI	42/3111 (1.4)	41/3016 (1.4)	1.00 (0.72–1.39)
Stage 1, 2, or 3	95/962 (9.9)	83/1052 (7.9)	1.29 (0.98–1.71)
AKI stage			
No AKI	42/3111 (1.4)	41/3016 (1.4)	1.00 (0.72–1.39)
Stage 1	15/558 (2.7)	16/610 (2.6)	1.08 (0.55–2.14)
Stage 2	38/201 (18.9)	27/214 (12.6)	1.49 (0.94–2.37)
Stage 3	42/203 (20.7)	40/228 (17.5)	1.21 (0.81–1.80)

No HTE by Initial Acidosis or Hyperlactatemia

	Balanced Fluid	0.9% Saline	Risk Ratio (95% CI)
	no. of events/total no. (%)		
Initial bicarbonate			
>=20 mEq/L	74/2565 (2.9)	63/2533 (2.5)	1.16 (0.85–1.60)
15–19 mEq/L	34/939 (3.6)	29/970 (3.0)	1.28 (0.78–2.09)
<15 mEq/L	19/195 (9.7)	26/205 (12.7)	0.92 (0.53–1.60)
Not measured	10/374 (2.7)	6/360 (1.7)	1.02 (0.59–1.75)
Initial blood lactate			
<2 mmol/L	29/1269 (2.3)	25/1292 (1.9)	1.21 (0.75–1.94)
2–5 mmol/L	40/1068 (3.7)	37/1022 (3.6)	1.04 (0.68–1.61)
>5 mmol/L	21/198 (10.6)	27/203 (13.3)	0.76 (0.45–1.29)
Not measured	47/1538 (3.1)	35/1551 (2.3)	1.23 (0.86–1.76)
Overall	137/4073 (3.4)	124/4068 (3.0)	1.10 (0.88–1.40)



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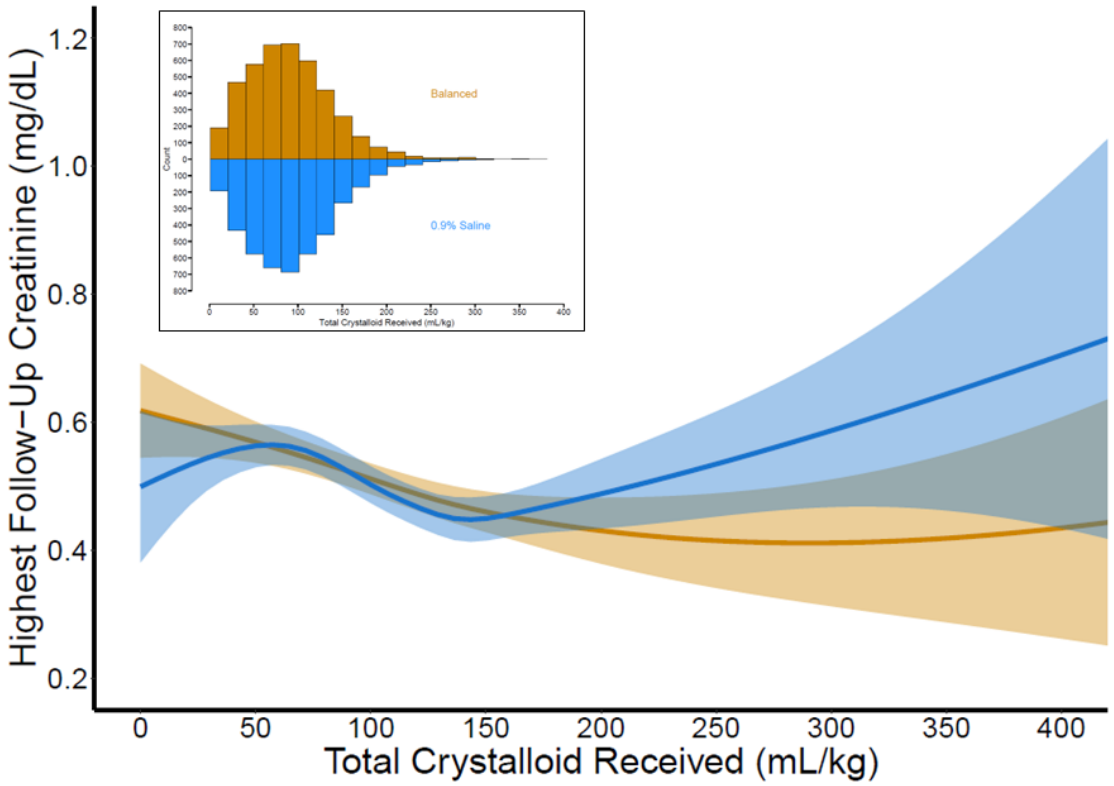
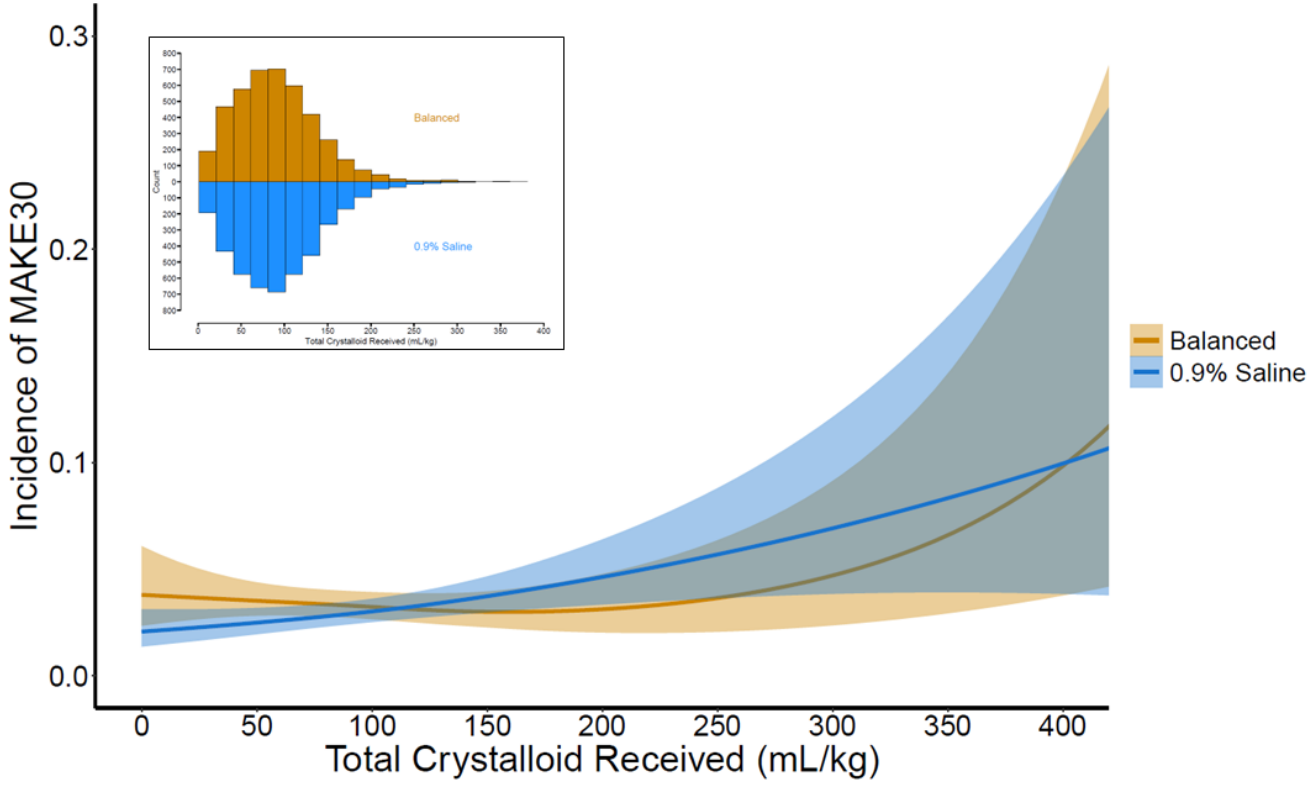
Effect of Fluid Volume on Kidney Function





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Secondary Analyses & Ancillary Studies

Multiple secondary analyses planned/in-progress

Impact of Crystalloid Fluid Type on Kidney Injury Biomarkers in Children Treated for Septic Shock

- *376 study participants from three US sites*
- *Urine NGAL, KIM-1, L-FABP, IL-18 and serum cystatin C at three timepoints*

NIH-funded Ancillary Studies

Julie Fitzgerald, MD PhD MSCE

Nadir Yehya, MD MSCE

Long-term Kidney Disease Outcomes in Children with Septic Shock (NIDDK)

- *Use computational phenotypes of CKD to measure long-term kidney outcomes through PEDSnet*

Finding Appropriate Subtypes in a Trial of Balanced versus Normal Saline Fluid in Sepsis (FAST-BOLUS; NIGMS)

- *Test for heterogeneity of treatment effect of fluid choice according to baseline mortality risk (PERSEVERE) & biologic sub-phenotypes*
- *Compare endothelial damage in septic children by fluid type*

Conclusions & Implications for Clinical Practice

- Among children treated for septic shock starting in an ED, no clinical differences for fluid resuscitation with balanced fluid or 0.9% saline
- Balanced fluid did mitigate hyperchloremia, but this did not translate to more patient-centered outcomes
- Both crystalloid fluid types were safe and effective
- **Clinicians should use most efficient, cost-effective fluid with consideration for balanced fluid if biochemical changes problematic**

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PRoMPT BOLUS
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Thank you!

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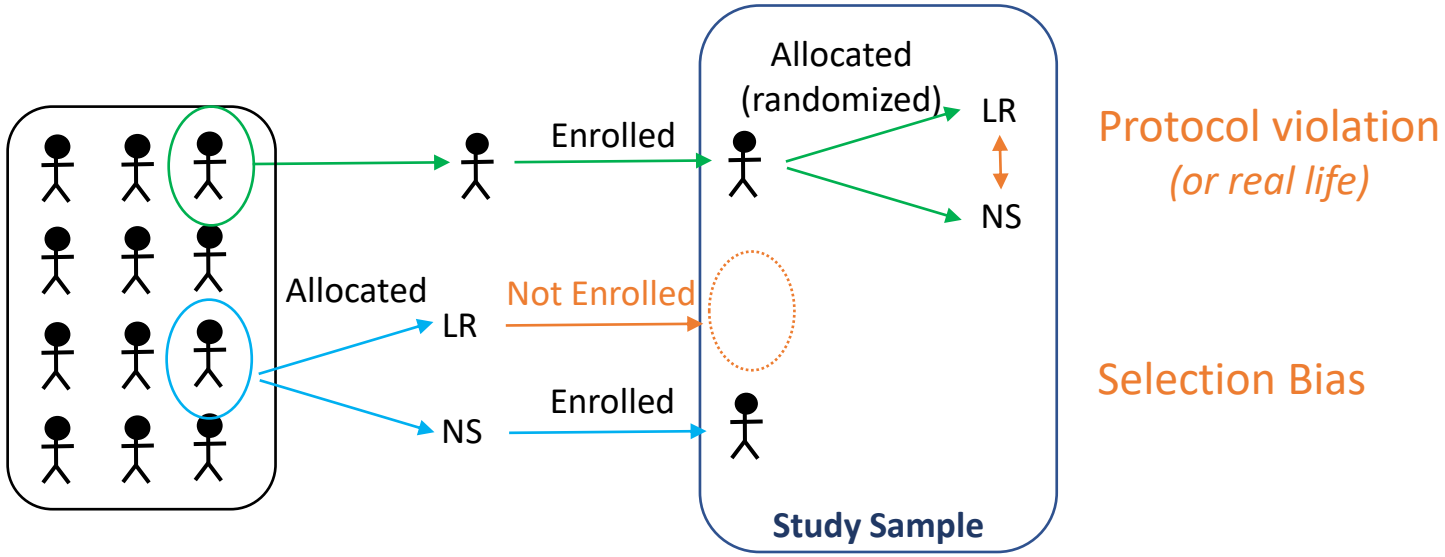
Why Patient Level Randomization?

- Options for treatment allocation:
  - Patient-level randomization after enrollment
  - Systematic allocation before enrollment (e.g., “every other month”)
- Awareness of allocation → selection bias
  - Personnel recruiting subjects could be affected
  - Subject’s willingness to enter study could be affected



Enrollment by Country

Country	Balanced Fluid	0.9% Saline
	(n =4,235)	(n = 4,247)
United States – n (%)	3,262 (77)	3,264 (77)
Canada – n (%)	367 (8.7)	360 (8.5)
Australia or New Zealand – n (%)	579 (14)	595 (14)
Costa Rica – n (%)	27 (0.64)	28 (0.66)

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No Effect Modification by Pre-Rand 0.9% Saline

Effect Modifier	Risk Ratio (95% CI)	*P* Value for Interaction
Pre-randomization 0.9% saline bolus		0.71
Yes	1.08 (0.81 to 1.45)	
No	1.20 (0.79 to 1.82)	
Pre-randomization 0.9% saline per 100 mL	--	0.92

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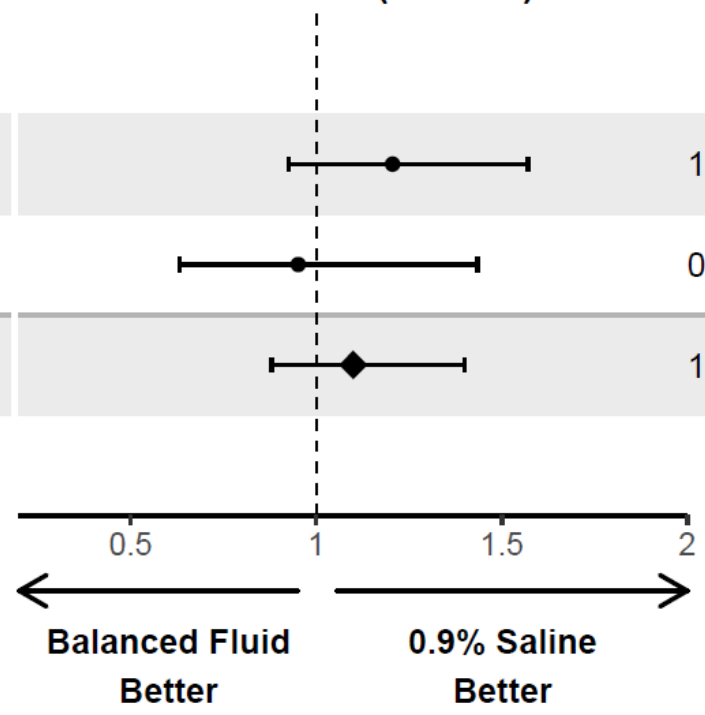
No HTE by Measured vs Imputed Baseline Creatinine

Baseline creatinine	Balanced Fluid *no. of events/total no. (%)*	0.9% Saline *no. of events/total no. (%)*	Risk Ratio (95% CI)
Measured	101/2448 (4.1)	88/2462 (3.6)	1.21 (0.93−1.57)
Imputed	36/1625 (2.2)	36/1606 (2.2)	0.95 (0.63−1.43)
Overall	137/4073 (3.4)	124/4068 (3.0)	1.10 (0.88−1.40)



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