FLUID RESUSCITATION: NEW CONCEPTS AND CONTROVERSY

Erik Stoltenberg, MD
Intensivist
Abbott Northwestern Critical Care Service
Allina Health Clinical Nursing Conference
February 25, 2020

Allina Health

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DISCLOSURES

- None

Outline and Objectives

- Case
- Learn Empiric Evidence for Specific Fluid Management Strategies
  - Goal-Directed Therapy and Hemodynamic Monitoring How?
  - Crystalloid vs colloid
  - Normal Saline vs. Lactated Ringer's What?
  - Specific Populations Who?
- Better Understand the Physiologic Basis of Fluid Therapy
- Return to case Why?

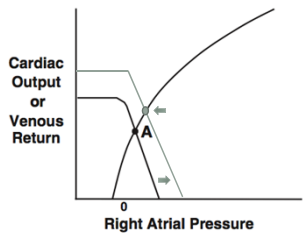
Case

72yo 80kg with h/o chronic kidney disease (Cr 1.2), HTN, and LVH with diastolic dysfunction

- presented with 3 days of fever, malaise, and hematuria – she was diagnosed with a UTI.
- hypotensive to SBP 80s (MAP 55) with HR in the 110s in the ED, lactate 3mmol/L, and is given 30mL/kg (2,400mL) normal saline
- Remains hypotensive, norepinephrine started to maintain MAP 65mmHg
- She clinically improves over the next 24h, and no longer requires norepinephrine
- the evening of hospital day 2 she is again hypotensive to SBPs 90s and UOP 10mL/hr over the last 2 hrs.

What should we do?

We'll use venous return physiology!



...And we'll RESUSCIATE the patient

- We want to do SOMETHING, and be AGGRESSIVE
- Give an additional 15mL/kg (~1L normal saline)

BUT HOW, EXACTLY, DO WE RESUSCITATE?

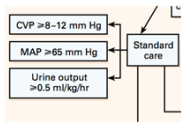
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

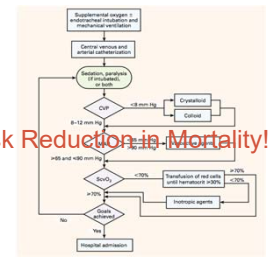
Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandria Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Pharm.D., and Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group*

- EGDT Trial (The Rivers Trial)
- N=263
- Detroit, MI
- Pts with severe sepsis (lactate >4) or septic shock (SBP<90) enrolled
- First 6h of therapy in the ED
- Average ScVO2 49% on admission!

E. Rivers et al., N Engl J Med 345, 1368–1377 (2001).

EGDT Protocol Comparison





16% Absolute Risk Reduction in Mortality!!!

5L crystalloid in 6h
Mortality 46.5%

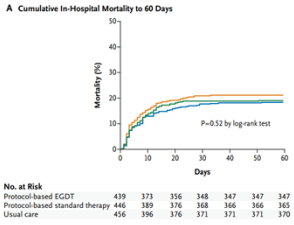
3.5L crystalloid in 6h
Mortality 30.5%

...EGDT revisited

- Since 2001, sepsis treatment has changed significantly:
  - Earlier detection
  - Earlier antibiotics
  - Greater appreciation for high mortality (30-60%!) of sepsis
  - Sepsis "bundles"
  - "code sepsis"/rapid response triggers
  - Better care integration from EMS to ED to ICU
- So is EGDT in sepsis still relevant? Unknown!
- Hence, further studies
  - ProCESS
  - ProMISe
  - ARISE
  - PRISM

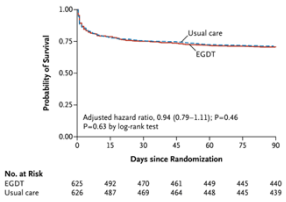
ProCESS: Protocolized Care for Early Septic Shock

- Published 2014 (enrolled 2008-2013)
- N=1341
- United States (31 centers)
- 3 arms:
  - Protocol-based EGDT (required CVC)
  - Protocol-based "standard care" (did not require CVC)
  - Standard care
- Primary outcome: 60-day mortality



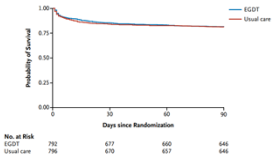
ProMISe: Protocolised Management in Sepsis

- Published 2015 (enrolled 2011-2014)
- n=1260
- England (56 centers)
- Primary outcome: 90 day mortality
- EGDT vs. usual-care
- EGDT required ScVO2 CVCs



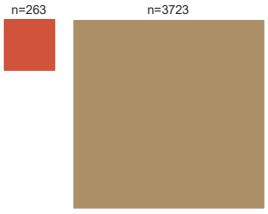
ARISE: Australasian Resuscitation in Sepsis Evaluation

- Published 2014 (enrolled 2008-2014)
- n=1600
- Australia and New Zealand (61 centers)
- Primary outcome 90 day mortality

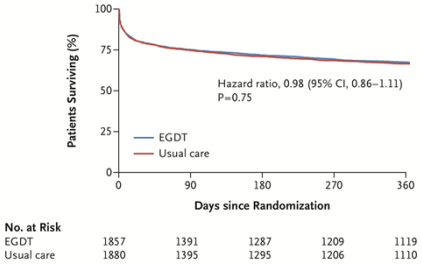


PRISM

- Meta-analysis of ProCESS, ProMISE, and ARISE
- N=3723
- Worldwide
- All trials had lower-than-expected mortality, limiting the strength of their conclusions



PRISM



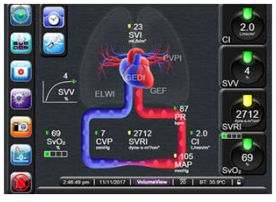
PRISM

"Even though a policy that mandates routine measurement of central venous pressure and central venous oxygen saturation in all patients with sepsis did not improve outcomes, **clinical judgment should always be applied** because, in specific circumstances, there may be a role for these measurements. The future of sepsis therapy may yet lie with **protocols that permit a more individualized approach** that is based on a greater understanding of the complex interplay among host genetics, individual pathophysiological features, and the infective agent."

The good physician treats the disease; the great physician treats the patient who has the disease.
—William Osler

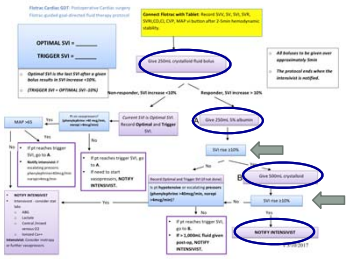
Post CV Surgery IVF therapy at ANW

- All patients after cardiac surgery for which a non-invasive cardiac output monitor (Edwards Flotrac) was valid
- N=1,137 over 2016-2017
  - 1 year of historical control vs.
  - 1 year of Flotrac-based resuscitation
- Crystalloid and albumin-based resuscitation



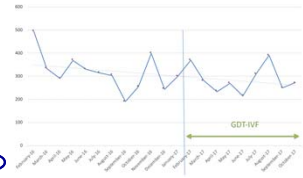
https://www.edwards.com/devices/hemodynamic-monitoring/ev1000

Post CV Surgery IVF therapy at ANW



Post CV Surgery IVF therapy at ANW
did not improve outcomes

	before protocol start	after protocol start	p-value
Hospital LOS (days)	6.1 (5.0, 9.0)	6.1 (5.0, 9.0)	0.71
ICU LOS (days)	1.1 (0.9, 2.1)	1.2 (1.0, 2.2)	0.98
Postoperative mechanical ventilation duration (hours)	4.1 (2.3, 6.6)	4.1 (2.6, 6.8)	0.40
New atrial fibrilation, n (%)	132 (22)	132 (25)	0.24
Hospital mortality, n (%)	9 (1)	3 (1)	0.15
Total cost, $1000	24.0 (20.3, 31.2)	24.5 (19.9, 32.6)	0.68
Postoperative 6% albumin volume, n - 0-48h	250 (250, 500)	250 (250, 500)	0.93
Postoperative 5% albumin volume - 0-24h	500 (250, 750)	500 (250, 750)	0.01



Albumin volume (mL) administration by month per patient

WITH WHAT, EXACTLY, DO WE RESUSCITATE?

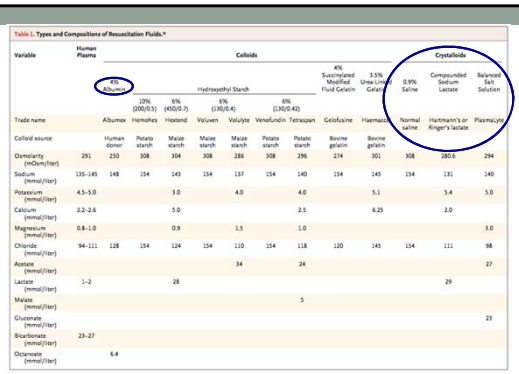


Table 1. Types and Compositions of Resuscitation Fluids.*

Variable	Human Plasma	Colloids								Crystalloids		
		4% Albumin	Hydroxyethyl Starch					4% Succinylated Modified Fluid Gelatin	3.5% Urea-Linked Gelatin	0.9% Saline	Compounded Sodium Lactate	Balanced Salt Solution
			10% (200/0.5)	6% (450/0.7)	6% (130/0.4)		6% (130/0.42)					
Trade name		Albumex	Hemohes	Hextend	Voluven	Volulyte	VenofundinTetraspan	Gelofusine	Haemaccel	Normal saline	Hartmann's or Ringer's lactate	Plasmalyte
Colloid source		Human donor	Potato starch	Maize starch	Maize starch	Maize starch	Potato starch	Potato starch	Bovine gelatin	Bovine gelatin			
Osmolarity (mOsm/liter)	291	250	308	154	308	286	308	296	274	301	308	280.6	294
Sodium (mmol/liter)	135–145	148	154	143	154	137	154	140	154	145	154	131	140
Potassium (mmol/liter)	4.5–5.0			3.0		4.0		4.0		5.1		5.4	5.0
Calcium (mmol/liter)	2.2–2.6			5.0				2.5		6.25		2.0	
Magnesium (mmol/liter)	0.8–1.0			0.9		1.5		1.0					3.0
Chloride (mmol/liter)	94–111	128	154	124	154	110	154	118	120	145	154	111	98
Acetate (mmol/liter)						34		24					27
Lactate (mmol/liter)	1–2			28								29	
Malate (mmol/liter)								5					
Gluconate (mmol/liter)													23
Bicarbonate (mmol/liter)	23–27												
Octanoate (mmol/liter)		6.4											

Crystalloids vs. Colloids

- A mythical debate
- Albumin (250mL):~$30-70/dose
- Crystaloid (1L): ~$1-2/dose (or less)
- Voluven (hydroxyethyl starch): ~$10/dose
- Many, many patients involved in many, many studies

ORIGINAL ARTICLE

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

The SAFE Study Investigators*

- 6997 patients in Australia and NZ
- 28 days of resuscitation
- 4% Albumin vs. normal saline

SAFE

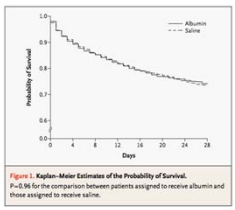
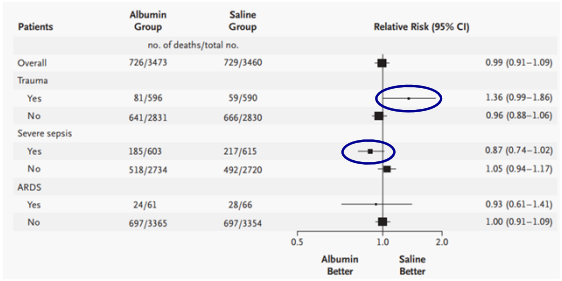


Figure 1. Kaplan–Meier Estimates of the Probability of Survival.
P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.

- CVP increased more in the albumin group
- More RBCs given in the albumin group
- Volume ratio of albumin to saline: 1:1.4 (not 1:3)

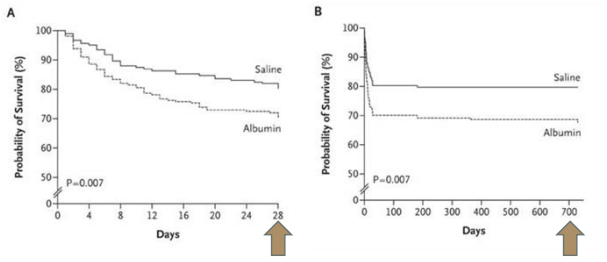
SAFE: Subgroups



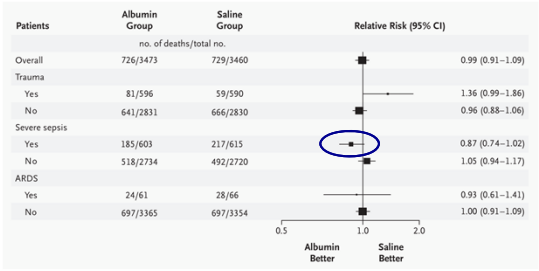
Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)

0.5 1.0 2.0
Albumin Better Saline Better

SAFE: Traumatic Brain Injury



SAFE: Severe Sepsis



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0.5 1.0 2.0
Albumin Better Saline Better

SAFE: albumin better in sepsis? hence ALBIOS

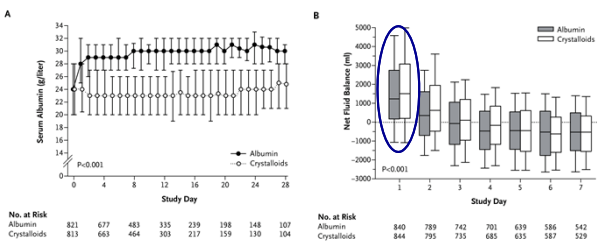
SAFE severe sepsis subgroup, mortality was:

- 30.7% in albumin group albumin group
- 35.3% in the normal saline group

ALBIOS (ALBumin Italian Outcome Sepsis) trial:

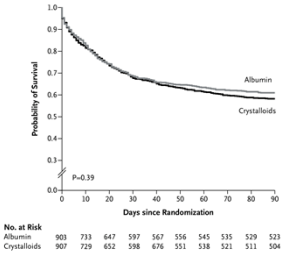
- 20% albumin + crystalloid vs. crystalloid alone
- N=1818 patients with severe sepsis in 100 ICUs in Italy
- Albumin daily given to maintain albumin 3g/dL
- Primary outcome: 28 day mortality

ALBIOS: albumin and fluid balance results

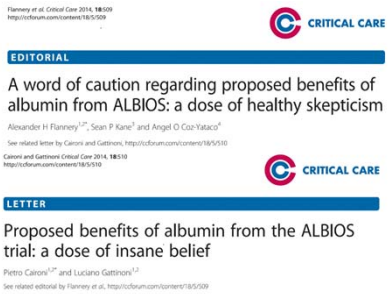


ALBIOS: primary outcome (mortality)

- 28 day mortality
  - 31.8% in albumin group
  - 32% in crystalloid group
- 90 day mortality
  - 41.1% in albumin group
  - 43.6% in crystalloid group
- Albumin group had:
  - higher blood pressure (MAP)
  - lower vasopressor use
  - Lower 90 day mortality in subgroup of patients with septic shock



ALBIOS generated much controversy



…hydroxyethyl starch?

- Probably no longer relevant, at least in the US

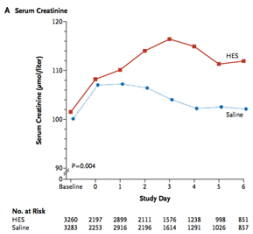
ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

- Same group as SAFE
- 7000 patients, diverse ICU patients
- Primary outcome 90 day mortality
  - No difference in primary outcome

J. A. Myburgh et al., N Engl J Med 367, 1901–1911 (2012).

HES vs. Saline



- Risk of AKI was 34.6 vs 38% (higher in HES, p=0.007)
- Risk of RRT was 5.8% vs 7% (higher in HES group, p=0.04)

Normal Saline vs. Lactated Ringer's

- Very pertinent to hospital medicine and critical care
- Medical vs. Surgical culture clash

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Octanoate (mmol/liter)		6.4											

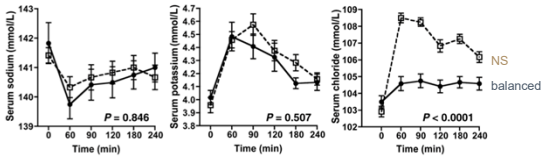
A Randomized, Controlled, Double-Blind Crossover Study on the Effects of 2-L Infusions of 0.9% Saline and Plasma-Lyte® 148 on Renal Blood Flow Velocity and Renal Cortical Tissue Perfusion in Healthy Volunteers

Abeed H. Chowdhury, BSc, MRCS, Eleanor F. Cox, PhD,† Susan T. Francis, PhD,† and Dileep N. Lobo, DM, FRCS, FACS**

- 20 healthy male volunteers given 2L NS
- Many, many variables observed and recorded

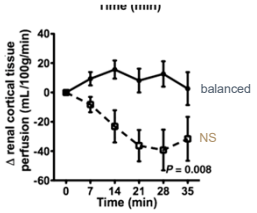
A. H. Chowdhury, E. F. Cox, S. T. Francis, D. N. Lobo, Annals of Surgery 256, 18–24 (2012).

Electrolyte Effects of NS



A. H. Chowdhury, E. F. Cox, S. T. Francis, D. N. Lobo, Annals of Surgery 256, 18–24 (2012).

Renal Effects of NS



A. H. Chowdhury, E. F. Cox, S. T. Francis, D. N. Lobo, Annals of Surgery 256, 18–24 (2012).

Does this matter (clinically)?

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Nor'azim Mohd Yunos, MD
Rinaldo Bellomo, MD, FCICM
Colin Hegarty, BSc
David Story, MD

Context Administration of traditional chloride-liberal intravenous fluids may precipitate acute kidney injury (AKI).

Objective To assess the association of a chloride-restrictive (vs chloride-liberal) intravenous fluid strategy with AKI in critically ill patients.

- Before/after study in Australia (2008/2009)
- 760pts vs 773pts
- Before: chloride-rich fluids allowed
- After: (6 months later) no chloride-rich fluids
- Primary Outcome: Cr rise and AKI risk

N. M. Yunos et al., JAMA: The Journal of the American Medical Association 308, 1566–1572 (2012).

Results

- Total chloride decreased by 144,504mmol
- After covariate adjustment, OR of AKI was 0.52 (14% vs. 8.4%) after chloride-rich fluids
- No differences in mortality, hospital length of stay, or ICU length of stay, or long term RRT need

Results, continued

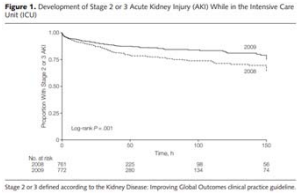


Figure 1. Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)

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

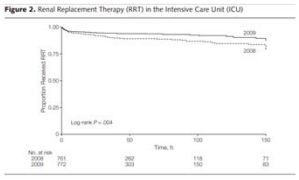


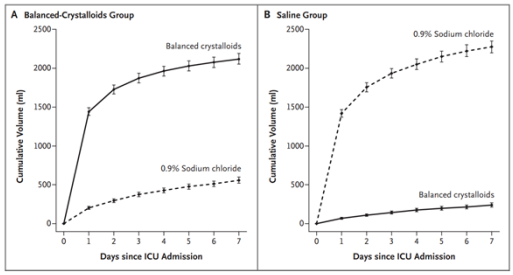
Figure 2. Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)

Enter: SMART-MED and SMART-SURG

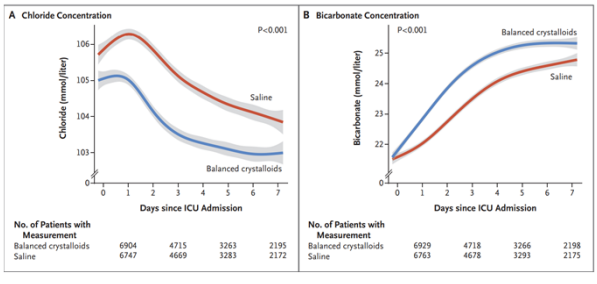
- "pragmatic, cluster-randomized, multiple-crossover trial"
- Published 2018 (enrolled 2015-2017)
- N=15,802 in 5 ICUs at Vanderbilt
- Waived informed consent
- 2 arms, with whole ICUs alternating monthly
  - LR or Plasmalyte
  - NS
- Primary outcome: "major kidney event"
  - death,
  - renal replacement therapy (RRT)/dialysis
  - persistent kidney dysfunction

*small note: patients with TBI could receive NS over balanced crystalloid, regardless of randomization

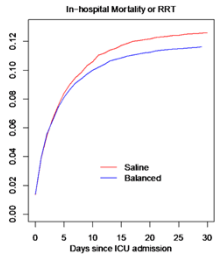
SMART: Results



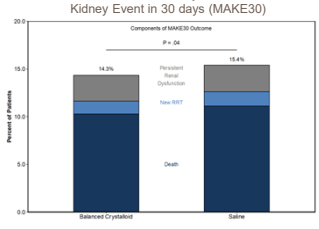
SMART: Results



SMART: Conclusions



Absolute outcome difference: 1.1% increased risk of Major Adverse Kidney Event in 30 days (MAKE30)



SMART: Conclusion

"The trial[s] presented here inform that thinking but do not provide unequivocal clinical direction."

1) But, jeez, it's hard to ignore!
2) Is there *really* any risk in AVOIDING Normal Saline?

Myburgh, J. Patient-Centered Outcomes and Resuscitation Fluids. N Engl J Med 378, 862–863 (2018).

But what about IVF in sepsis?

SMART: Secondary Analysis in Sepsis

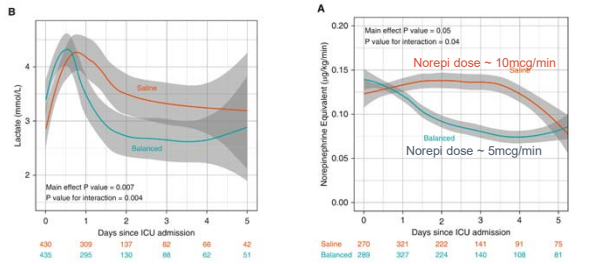
- N=1641
- Primary outcome now mortality

SMART: Secondary Analysis in Sepsis

Outcome*	*n*	Balanced Crystalloids (*n* = 824)	Saline (*n* = 817)	Adjusted OR (95% CI)†
Primary outcome				
30-d in-hospital mortality, *n* (%)	1,641	217 (26.3)	255 (31.2)	0.74 (0.59 to 0.93)
Additional clinical outcomes				
60-d in-hospital mortality, *n* (%)	1,641	241 (29.2)	269 (32.9)	0.80 (0.64 to 1.01)
ICU-free days‡, median (IQR)	1,641	23 (0 to 26)	23 (0 to 26)	1.15 (0.97 to 1.38)
Mean ± SD	—	17 ± 11	16 ± 12	—
Ventilator-free days‡, median (IQR)	1,641	27 (0 to 28)	26 (0 to 28)	1.37 (1.12 to 1.68)
Mean ± SD	—	19 ± 12	18 ± 13	—
Vasopressor-free days‡, median (IQR)	1,641	27 (0 to 28)	27 (0 to 28)	1.25 (1.02 to 1.54)
Mean ± SD	—	20 ± 12	19 ± 13	—
Renal replacement therapy–free days‡, median (IQR)	1,641	28 (0 to 28)	28 (0 to 28)	1.35 (1.08 to 1.69)
Mean ± SD	—	20 ± 12	19 ± 13	—
Additional renal outcomes§				
Major adverse kidney event within 30 d, *n* (%)‖	1,641	292 (35.4)	328 (40.1)	0.78 (0.63 to 0.97)
Receipt of new renal replacement therapy, *n* (%)¶	1,458	54 (7.4)	75 (10.3)	0.71 (0.48 to 1.04)
Final creatinine >200% of baseline, *n* (%)	1,458	164 (22.4)	162 (22.3)	0.99 (0.76 to 1.28)
Stage II or greater AKI developing after ICU admission, *n* (%)**	1,458	201 (27.4)	231 (31.9)	0.79 (0.63 to 1.00)
Creatinine††, mg/dl	1,458			
Highest before discharge or 30 d	—	1.58 (0.87 to 3.00)	1.59 (0.93 to 2.97)	0.95 (0.79 to 1.13)
Change from baseline to highest value	—	0.18 (−0.07 to 1.13)	0.23 (−0.07 to 1.20)	0.99 (0.82 to 1.18)
Final value before discharge or 30 d	—	0.94 (0.69 to 1.77)	0.85 (0.71 to 1.80)	0.97 (0.81 to 1.16)

4.9% absolute difference (NNT 20)

SMART: Secondary Analysis in Sepsis



What about the Surviving Sepsis Guidelines?

"The use of IV fluids in the resuscitation of patients is a cornerstone of modern therapy. Despite this, there is *little available evidence* from RCTs to support its practice; this is an area in which research is urgently needed."

What about the Surviving Sepsis Guidelines?

- "We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (Best Practice Statement).
- We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
- We suggest using either balanced crystalloids or saline*** for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
- We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence)."

*** recommendation made before results of SMART (LR vs. NS) Trial

SO WHEN AND HOW MUCH FLUID?

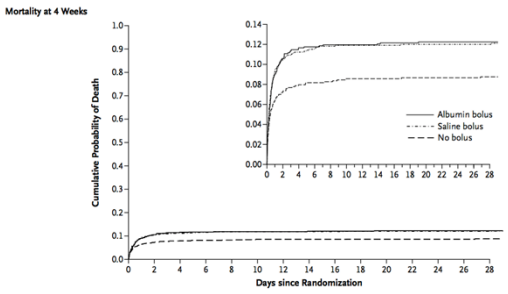
What about fluid boluses at all?

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med., Robert O. Opoka, M.B., Ch.B., M.Med.,

- Children with febrile illness in Sub-Saharan Africa
- 2 strata (1 with hypotension, 1 without),
- 3 groups (20-40mL/kg albumin bolus, crystalloid bolus, 0.9% saline maintenance only)
- rates of death 10.6%, 10.5%, 7.3%, OR 1.44 (1.09-1.9)



How about risks of fluids?

ORIGINAL ARTICLE

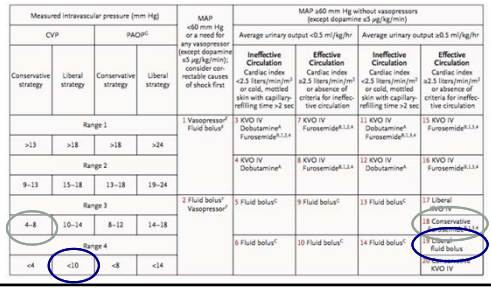
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

- 2x2 factorial trial with PAC vs. CVP
- 1000 patients with ARDS
- Fluid balance during 7 days was +7L vs. 0L

National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network et al., N Engl J Med 354, 2564–2575 (2006).

CVP-based conservative vs. liberal fluid strategy improves outcomes



Measured intravascular pressure (mm Hg)				MAP <60 mm Hg or a need for any vasopressor (except dopamine ≤5 μg/kg/min); consider correctable causes of shock first	MAP ≥60 mm Hg without vasopressors (except dopamine ≤5 μg/kg/min)			
CVP		PAOP[G]			Average urinary output <0.5 ml/kg/hr		Average urinary output ≥0.5 ml/kg/hr	
Conservative strategy	Liberal strategy	Conservative strategy	Liberal strategy		Ineffective Circulation Cardiac index <2.5 liters/min/m² or cold, mottled skin with capillary-refilling time >2 sec	Effective Circulation Cardiac index ≥2.5 liters/min/m² or absence of criteria for ineffective circulation	Ineffective Circulation Cardiac index <2.5 liters/min/m² or cold, mottled skin with capillary-refilling time >2 sec	Effective Circulation Cardiac index ≥2.5 liters/min/m² or absence of criteria for ineffective circulation
Range 1				3 Vasopressor[F] Fluid bolus[A]	3 KVO IV Dobutamine[A] Furosemide[B,1,2,A]	7 KVO IV Furosemide[B,1,2,A]	11 KVO IV Dobutamine[A] Furosemide[B,1,3,A]	15 KVO IV Furosemide[B,1,3,A]
>13	>18	>18	>24					
Range 2					4 KVO IV Dobutamine[A]	8 KVO IV Furosemide[B,1,2,A]	12 KVO IV Dobutamine[A]	16 KVO IV Furosemide[B,1,3,A]
9–13	15–18	13–18	19–24					
Range 3				2 Fluid bolus[F] Vasopressor[F]	5 Fluid bolus[C]	9 Fluid bolus[C]	13 Fluid bolus[C]	17 Liberal KVO IV
4–8	10–14	8–12	14–18					18 Conservative Furosemide[B,1,3,A]
Range 4					6 Fluid bolus[C]	10 Fluid bolus[C]	14 Fluid bolus[C]	19 Liberal fluid bolus
<4	<10	<8	<14					KVO IV

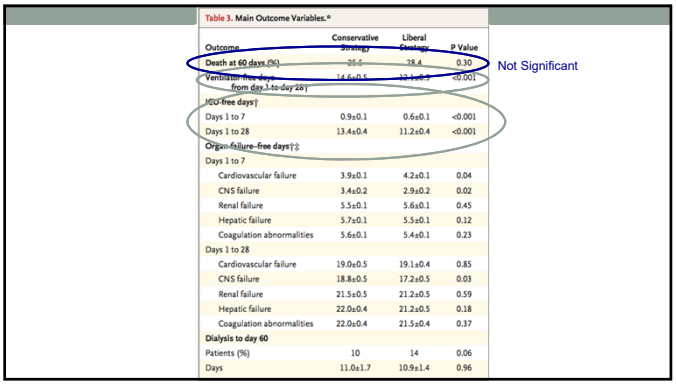


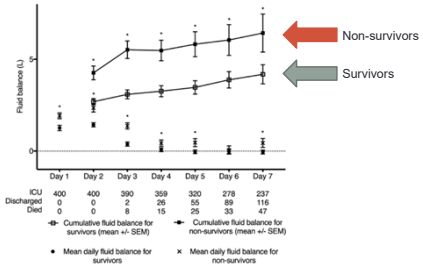
Table 3. Main Outcome Variables.*

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days, from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Organ-failure–free days†‡			
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
CNS failure	3.4±0.2	2.9±0.2	0.02
Renal failure	5.5±0.1	5.6±0.1	0.45
Hepatic failure	5.7±0.1	5.5±0.1	0.12
Coagulation abnormalities	5.6±0.1	5.4±0.1	0.23
Days 1 to 28			
Cardiovascular failure	19.0±0.5	19.1±0.4	0.85
CNS failure	18.8±0.5	17.2±0.5	0.03
Renal failure	21.5±0.5	21.2±0.5	0.59
Hepatic failure	22.0±0.4	21.2±0.5	0.18
Coagulation abnormalities	22.0±0.4	21.5±0.4	0.37
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96

Not Significant

A new concept: De-resuscitation

A new concept: De-resuscitation



TO SUMMARIZE...

Historical Perioperative Fluid Fundamentals

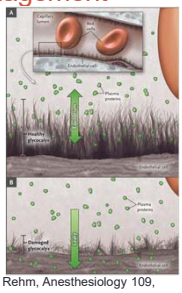
- Fasted patients are hypovolemic
- Insensible perspiration increases dramatically during surgery
- Third space losses require generous substitution
- Hypervolemia is harmless because the kidneys regulate the overload

=LOTS OF FLUID GIVEN!!

- 5mL/kg/h
- 10mL/kg/h
- 15mL/kg/h!!

Rational Critical Care Fluid Management

- Should we maximize preload to maximize stroke volume?
- restrictive vs. liberal IVF
- "In practice, adequate volume is usually defined by hemodynamic stability, because there is no routine clinical method for evaluating tissue perfusion."
- Fluid is not benign



D. Chappell, M. Jacob, K. Hofmann-Kiefer, P. Conzen, M. Rehm, Anesthesiology 109, 723–740 (2008).

Conclusions of a Recent Review:

- Fluids should be administered with the same caution as any other IV drug
- Consider cumulative fluid balance and actual body weight when selecting the dose of resuscitation fluid
- Consider vasoactive agents early in the treatment of shock
- Fluid requirements change over time in critically ill patient
- Oliguria is a normal response to hypovolemia and should not be used soley as a trigger or end point for fluid resuscitation, especially in the post-resuscitaiton period (>24h)
- The role of hypotonic maintenance fluids is questionable once dehydration has been corrected
- Isotonic, balanced salt solutions are pragmatic initial resuscitation fluid for the majority of acutely ill patients

J. A. Myburgh, M. G. Mythen, N Engl J Med 369, 1243–1251 (2013).

Return to Objectives

- How?
  - EGDT is ingrained in our care, but specific protocol unlikely to improve outcomes
  - Treat IV fluids like any other drug therapy!
  - Continued improvement in critical care and sepsis care is essential (and we've improved so much already…)
- What?
  - Balanced crystalloids (LR) over normal saline
  - Balanced crystalloids to albumin
- Who?
  - critically-ill septic patients: consider LR (and albumin perhaps sometimes)
  - patients with traumatic brain injury: avoid albumin (and probably hypotonic fluids)
- When?
  - Resuscitate QUICKLY (right away and run fluids fast)
  - Use this information NOW!
- Why?
  - To save lives!

Case Revisited

She is now hospital day 4. Her vital signs have been normal for the last 48h, save for still requiring O2 by NC at 3L/min with SpO2=95%. Her UOP has been 20mL/hr for the last 4hrs. She has moderate diffuse edema, and she is 4kg up from admission.

What would you do?

- On presentation, give LR quickly and assess for effectiveness/volume responsiveness* with every bolus
  - *many ways to test effectiveness/volume responsiveness, none of them perfect
- STOP boluses when ineffective or when patient improves
- Early use of vasopressors (and other strategies to manage hypotension)
- Avoid MIVF unless clinically deHYDRATED
- Watch obligate input with IV medications/infusions
- Consider diuresis early
- Give this poor woman some furosemide!

THANK YOU!

References

1. ARISE Investigators et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 371, 1496–1506 (2014).
2. Brown, The Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. Am J Respir Crit Care Med 200, 1487–1495 (2019).
3. Caironi, P. et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 370, 1412–1421 (2014).
4. Chong, M. A., Wang, Y., Berbenetz, N. M. & McConachie, I. Does goal-directed haemodynamic and fluid therapy improve peri-operative outcomes?: A systematic review and meta-analysis. European Journal of Anaesthesiology 35, 469–483 (2018).
5. Chowdhury, A. H., Cox, E. F., Francis, S. T. & Lobo, D. N. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Annals of Surgery 256, 18–24 (2012).
6. Finfer, S. et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350, 2247–2256 (2004).
7. Flannery, A. H., Kane, S. P. & Coz-Yataco, A. O. A word of caution regarding proposed benefits of albumin from ALBIOS: a dose of healthy skepticism. Crit Care 18, 1412 (2014).
8. Maitland, K. et al. Mortality after Fluid Bolus in African Children with Severe Infection. N Engl J Med 364, 2483–2495 (2011).
9. Mouncey, P. R. et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372, 1301–1311 (2015).
10. Myburgh, J. A. & Mythen, M. G. Resuscitation fluids. N Engl J Med 369, 1243–1251 (2013).
11. Myburgh, J. A. et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. N Engl J Med 367, 1901–1911 (2012).
12. Myburgh, J. Patient-Centered Outcomes and Resuscitation Fluids. N Engl J Med 378, 862–863 (2018).
13. Myles, P. S. et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. N Engl J Med 378, 2263–2274 (2018).
14. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354, 2564–2575 (2006).
15. Osawa, E. A. et al. Effect of Perioperative Goal-Directed Hemodynamic Resuscitation Therapy on Outcomes Following Cardiac Surgery: A Randomized Clinical Trial and Systematic Review. Critical Care Medicine 44, 724–733 (2016).
16. PRISM Investigators. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. N Engl J Med 376, 2223–2234 (2017).
17. Pietro Caironi & Gattinoni, L. Proposed benefits of albumin from the ALBIOS trial: a dose of insane belief. Crit Care 18, 1–1 (2014).

References

17. ProCESS Investigators et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 370, 1683–1693 (2014).
18. Rhodes, A. et al. Surviving Sepsis Campaign. Critical Care Medicine 45, 486–552 (2017).
19. Rivers, E. et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345, 1368–1377 (2001).
20. SAFE Study Investigators et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 357, 874–884 (2007).
21. Self, W. H. et al. Balanced Crystalloids versus Saline in Noncritically Ill Adults. New England Journal of Medicine 378, 819–828 (2018).
22. Semler, M. W. et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 378, 829–839 (2018).
23. Silversides, J. A. et al. Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness. Critical Care Medicine 46, 1600–1607 (2018).
24. Yunos, N. M. et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA: The Journal of the American Medical Association 308, 1566–1572 (2012).

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