Golden Window of Fluid Administration in AKI: *What Type, When, and How Much*

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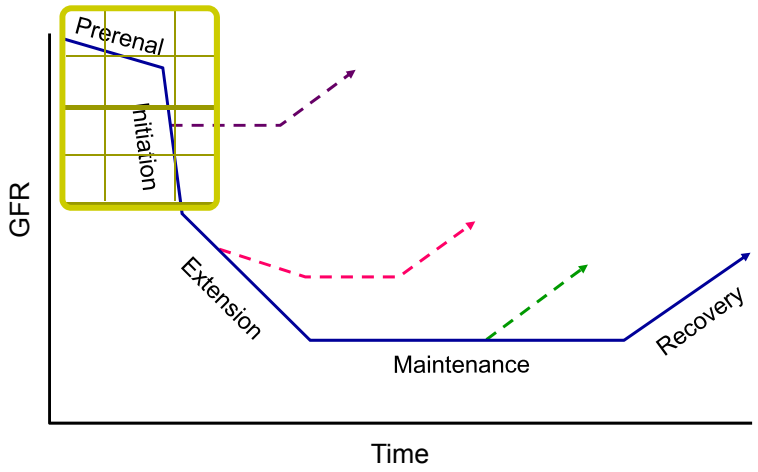
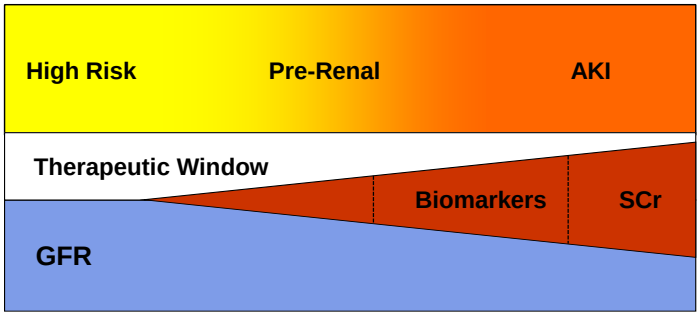
Conceptual Framework for the Treatment of AKI



Therapeutic Window for Prevention and Treatment of AKI

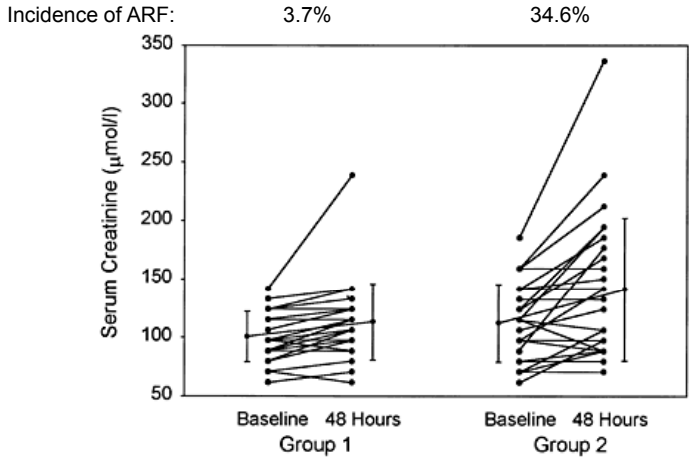


Jo SK, et al. Clin J Am Soc Nephrol 2007; 2:356-365

Clinical Settings where Volume Administration may Prevent AKI

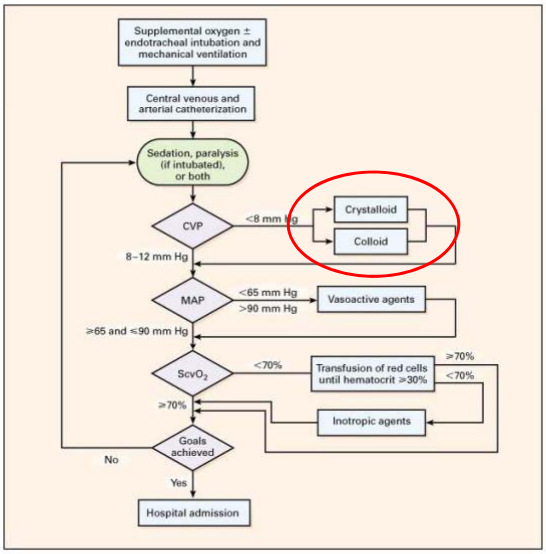
- Iodinated radiocontrast
- Rhabdomyolysis
- Aminoglycosides
- Amphotericin B
- Cis-platinium
- Acyclovir
- Tumor lysis syndrome
- Spontaneous bacterial peritonitis
- Many others…..

Isotonic Saline for Prevention of Radiocontrast-Induced AKI



Trivedi HS, et al. Nephron Clin Pract 2003; 93:c29-c34

Early Goal-Directed Therapy in Sepsis



Rivers E, et al. N Engl J Med 2001; 345: 1368-1377

Early Goal-Directed Therapy in Sepsis

	Standard of Care	EGDT	*P*-value
Total Fluid Administered (ml)			
hours 0-6	3,499±2,438	4,981±2,984	<0.001
hours 7-72	10,602±6,216	8,625±5,162	0.01
hours 0-72	13,358±7,729	13,443±6,390	0.73
RBC transfusion (%)			
hours 0-6	18.5	64.1	<0.001
hours 7-72	32.8	11.1	<0.001
hours 0-72	44.5	68.4	<0.001

Rivers E, et al. N Engl J Med 2001; 345: 1368-1377

Early Goal-Directed Therapy in Sepsis

	Standard of Care	EGDT	*P*-value
CVP (mm Hg)			
hour 6	11.8±6.8	13.8±6.8	0.007
hours 7-72	11.6±6.1	11.9±5.6	0.68
MAP (mm Hg)			
hour 6	81±18	95±19	<0.001
hours 7-72	80±15	87±15	<0.001
$S_{CV}O_2$ (%)			
hour 6	66.0±15.5	77.3±10.0	<0.001
hours 7-72	65.3±11.4	70.4±10.7	<0.001
Lactate (mmol/L)			
hour 6	4.9±4.7	4.3±4.2	0.01
hours 7-72	3.9±4.4	3.0±4.4	0.02

Rivers E, et al. N Engl J Med 2001; 345: 1368-1377

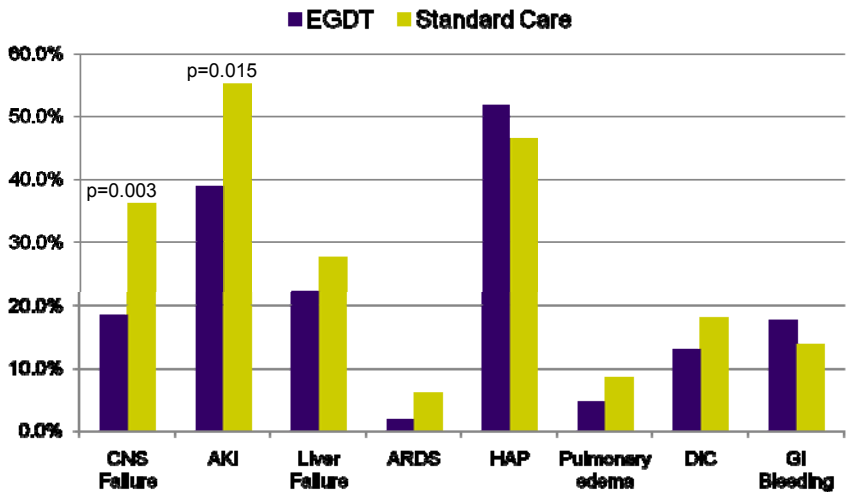
Early Goal-Directed Therapy in Sepsis

	Standard of Care (N=133)	EGDT (N=130)	*P*-value
APACHE II Score*	15.9±6.4	13.0±6.3	<0.001
MODS Score*	6.4±4.0	5.1±3.9	<0.001
Prothrombin time* (sec)	17.3±6.1	15.4±6.1	0.001
Fibrin split products* (µg/dl)	62.0±71.4	39.2±71.2	<0.001
Mechanical ventilation* (%)	16.8	2.6	<0.001
Mortality (%)			
In-hospital	46.5	30.5	0.009
28-day	49.2	33.3	0.01
60-day	56.9	44.3	0.03

* At 7 to 72 hours

Rivers E, et al. N Engl J Med 2001; 345: 1368-1377

Modified EGDT in Sepsis



Lin S-M, et al. Shock 2006; 26:551-557

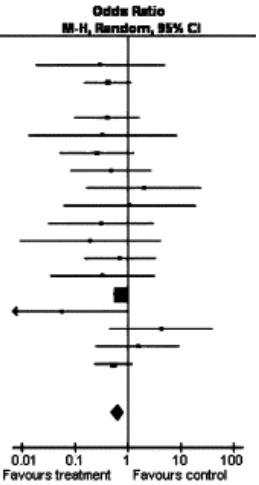
Early Goal-Directed Therapy in Sepsis

- EGDT endorsed as part of the Surviving Sepsis Campaign as B recommendation
- EGDT represents a bundle of care in which the relative benefit of individual components has not been validated
  - Use of central line for guiding therapy / CVP target
  - Blood transfusion
  - Use of $S_{CV}O_2$ versus blood lactate
- Results of the original single-center RCT now being re-examined in a multicenter RCT (ProCESS) comparing EGDT to protocolized standard care and usual care

Goal-Directed Perioperative Management

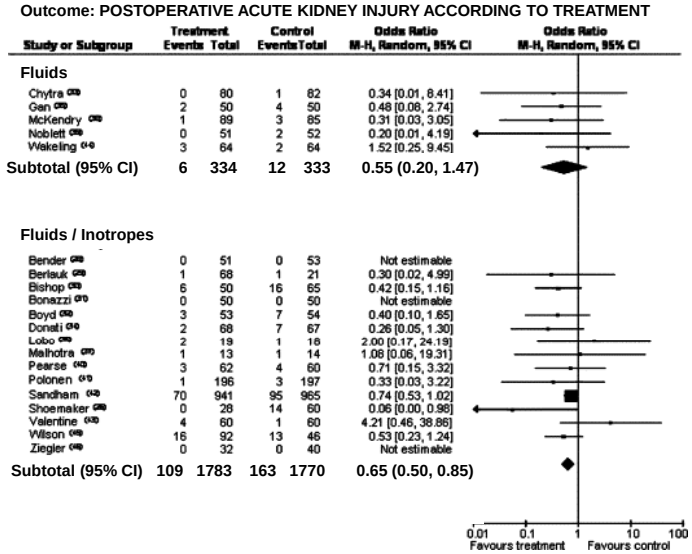
Outcome: POSTOPERATIVE ACUTE KIDNEY INJURY

Studies	Treatment Events	Treatment Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
Bender	0	51	0	53	Not estimable
Berlauk	1	68	1	21	0.30 [0.02, 4.99]
Bishop	6	50	16	65	0.42 [0.15, 1.16]
Bonazzi	0	50	0	50	Not estimable
Boyd	3	53	7	54	0.40 [0.10, 1.65]
Chytra	0	80	1	82	0.34 [0.01, 8.41]
Donati	2	68	7	67	0.26 [0.05, 1.30]
Gan	2	50	4	50	0.48 [0.08, 2.74]
Lobo	2	19	1	18	2.00 [0.17, 24.19]
Malhotra	1	13	1	14	1.08 [0.06, 19.31]
McKendry	1	89	3	85	0.31 [0.03, 3.05]
Noblett	0	51	2	52	0.20 [0.01, 4.19]
Pearse	3	62	4	60	0.71 [0.15, 3.32]
Polonen	1	196	3	197	0.33 [0.03, 3.22]
Sandham	70	941	95	965	0.74 [0.53, 1.02]
Shoemaker	0	28	14	60	0.06 [0.00, 0.98]
Valentine	4	60	1	60	4.21 [0.46, 38.86]
Wakeling	3	64	2	64	1.52 [0.25, 9.45]
Wilson	16	92	13	46	0.53 [0.23, 1.24]
Ziegler	0	32	0	40	Not estimable
Total (95% CI)	**115**	**2117**	**175**	**2183**	**0.64 (0.50, 0.83)**



Brienza N, et al. Crit Care Med 2009; 37: 2079-2090

Goal-Directed Perioperative Management



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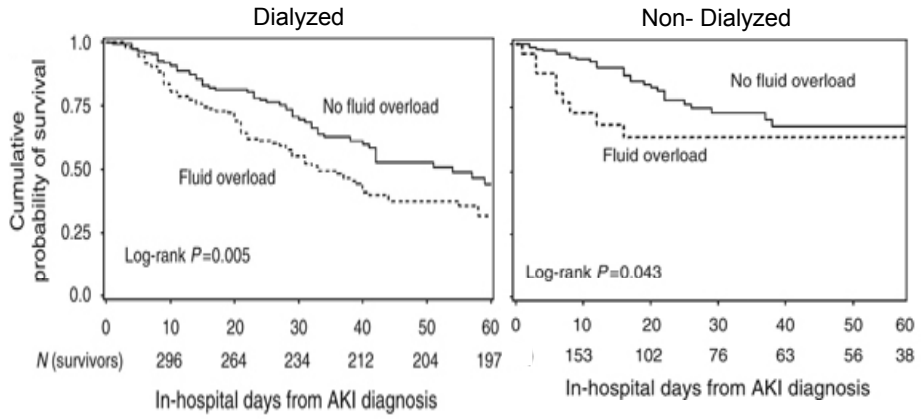
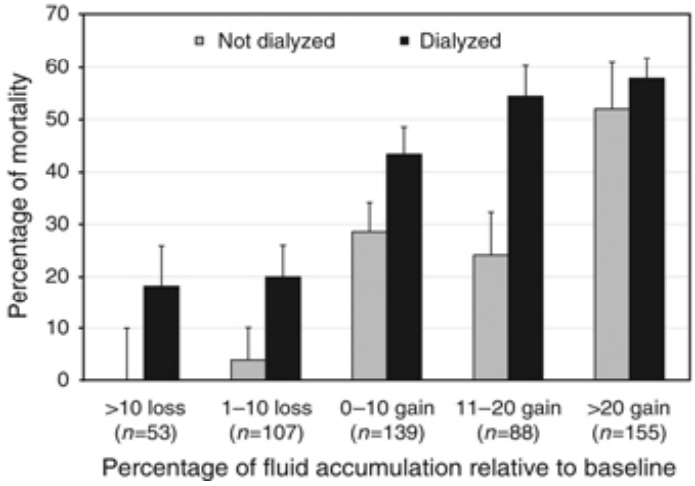
PICARD Study: Impact of Fluid Overload on Mortality



Bouchard J, et al. Kidney Int 2009; 76: 422-427

PICARD Study: Impact of Fluid Overload on Mortality



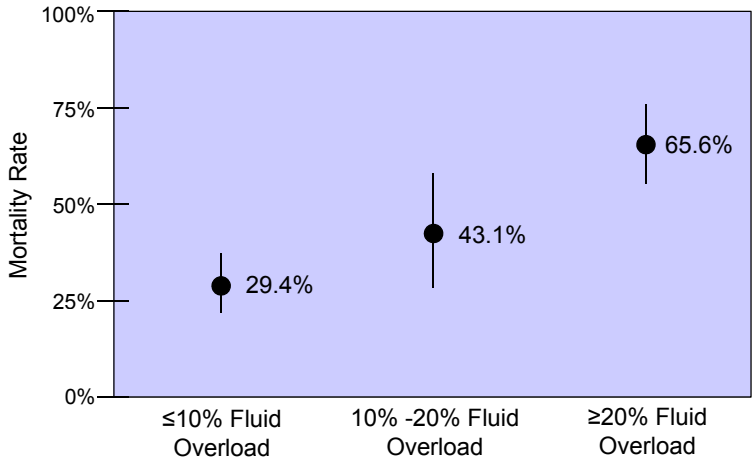
Bouchard J, et al. Kidney Int 2009; 76: 422-427

Fluid Balance and Outcomes in Sepsis Associated AKI

Mean daily fluid balance (L/24 hours)			
	Survivors	Non-survivors	P-value
ARF	0.15 ± 1.06	0.98 ± 1.50	<0.001
Early ARF	0.14 ± 1.05	1.19 ± 1.48	<0.001
Late ARF	0.11 ± 1.03	0.39 ± 1.40	0.06

Payen D, et al. Critic Care 2008; 12:R74

Mortality and Fluid Overload in Pediatric CRRT Patients



Sutherland SM, et al. Am J Kidney Dis 2010; 55:316-325

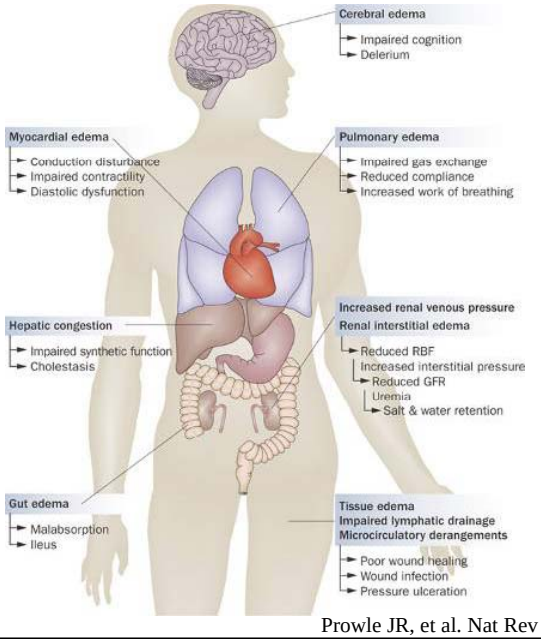
Mortality and Fluid Overload in Pediatric CRRT Patients

Multivariate Model

Variable	Odds Ratio	95% CI
Diagnosis of MODS	4.7	2.0 – 10.6
Oncologic diagnosis	3.2	1.6 – 6.1
Percentage of fluid overload		
as continuous variable	1.03	1.01 – 1.05
as dichotomous variable (<20% vs. ≥20%)	8.5	2.8 - 25.7

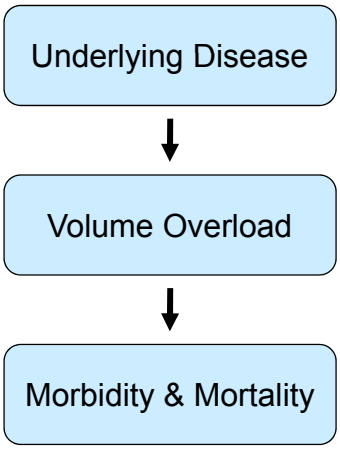
Sutherland SM, et al. Am J Kidney Dis 2010; 55:316-325

Sequelae of Fluid Overload

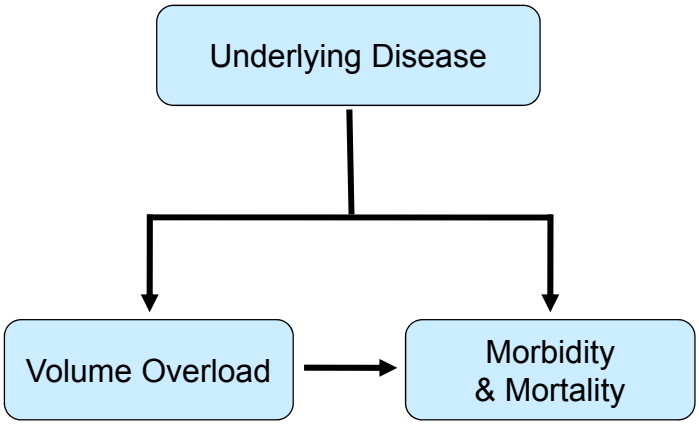


Prowle JR, et al. Nat Rev Nephrol 2010; 6:107-115

Fluid Balance, Morbidity & Mortality



Fluid Balance, Morbidity & Mortality

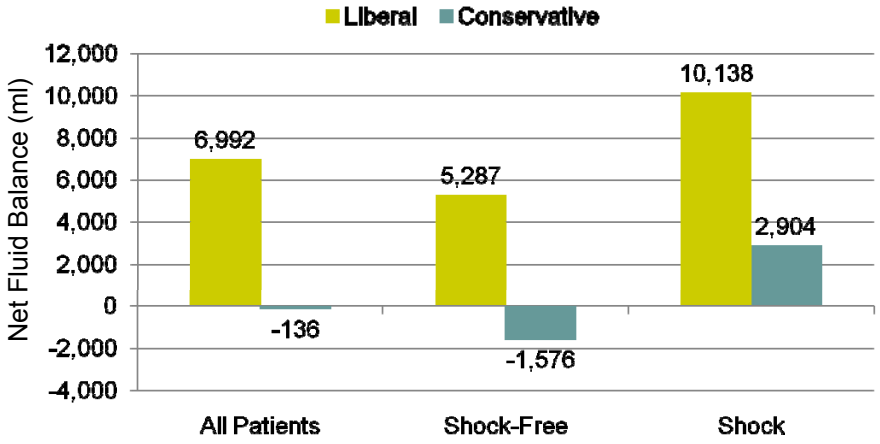


ARDS Network: Fluid and Catheter Treatment Trial

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				1 Vasopressor[F] Fluid bolus[F]	3 KVO IV Dobutamine[A] Furosemide[B,1,2,4]	7 KVO IV Furosemide[B,1,2,4]	11 KVO IV Dobutamine[A] Furosemide[B,1,3,4]	15 KVO IV Furosemide[B,1,3,4]
>13	>18	>18	>24					
Range 2					4 KVO IV Dobutamine[A]	8 KVO IV Furosemide[B,1,2,4]	12 KVO IV Dobutamine[A]	16 KVO IV Furosemide[B,1,3,4]
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,1,3,4]
Range 4					6 Fluid bolus[C]	10 Fluid bolus[C]	14 Fluid bolus[C]	19 Liberal fluid bolus
<4	<10	<8	<14					20 Conservative KVO IV

Wiedemann HP, et al. N Engl J Med 2006; 354: 2564-2575

ARDS Network: FACTT Study – Fluid Balance at Day 7



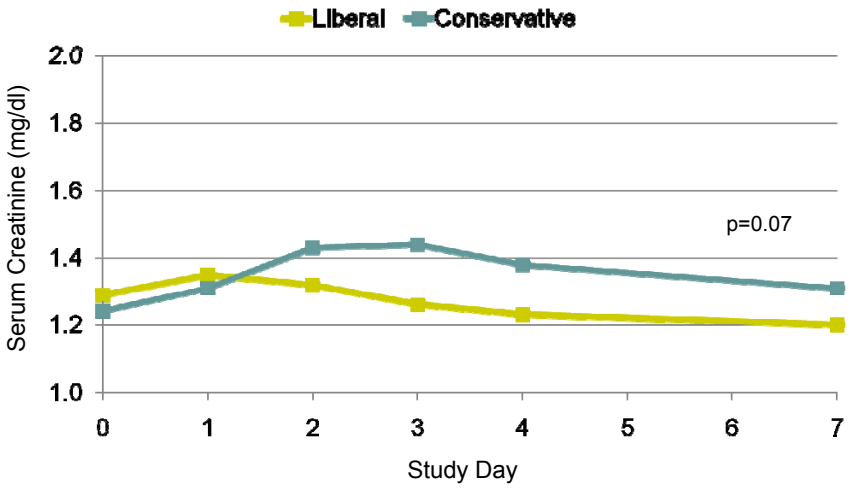
Wiedemann HP, et al. N Engl J Med 2006; 354: 2564-2575

ARDS Network: FACTT Study – Outcomes

Outcome	Conservative Strategy	Liberal Strategy	P-Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days through 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
Renal failure-free days (SCr < 2 mg/dl)			
days 1 to 7	5.5±0.1	5.6±0.1	0.45
days 1 to 28	21.5±0.5	21.2±0.5	0.59
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96

Wiedemann HP, et al. N Engl J Med 2006; 354: 2564-2575

ARDS Network: FACTT Study- Kidney Function

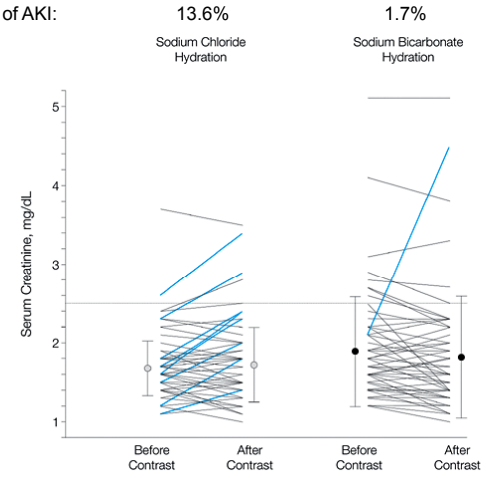


Wiedemann HP, et al. N Engl J Med 2006; 354: 2564-2575

Selection of Fluids

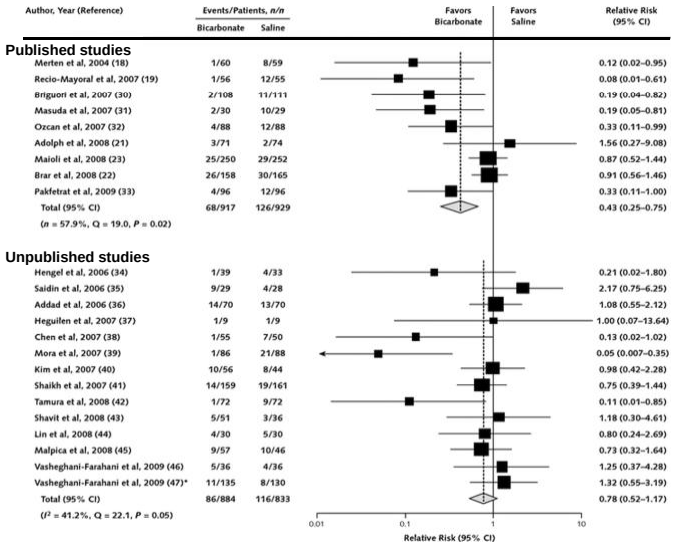
- Crystalloid
  - Saline
  - Bicarbonate
  - “Physiologic” formulations (e.g, lactated Ringer’s)
- Colloid
  - Albumin
  - Starch
  - Gellatin

Sodium Bicarbonate versus Saline Prophylaxis of CIN



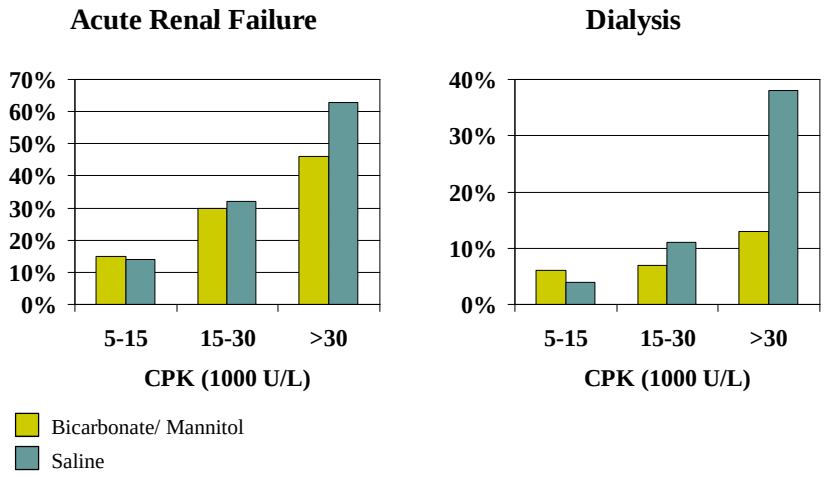
Merten GJ, et al. JAMA 2004; 291:2328-2334

Sodium Bicarbonate versus Saline Prophylaxis of CIN: Meta Analysis



Zoungas S et al. Ann Intern Med 2009;151:631-638

Prevention of Myoglobinuric AKI Role of Mannitol and Bicarbonate



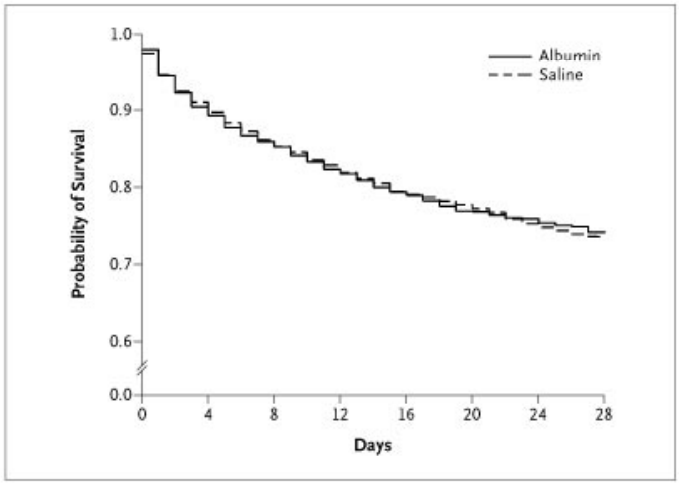
Brown CVR, et al. J Trauma 2004; 56:1191-1196

Comparison of Albumin versus Saline: The SAFE Study

Outcome	Albumin Group (N=3473)	Saline Group (N=3460)	*P*-value
Status at 28 days (%)			
Dead	20.9%	21.1%	0.87
Alive in ICU	3.2%	2.5%	0.09
Alive in hospital	22.8%	24.5%	0.10
ICU length of stay (days)	6.5±6.6	6.2±6.2	0.44
Hospital length of stay (days)	15.3±9.6	15.6±9.6	0.30
Duration of mechanical ventilation (days)	4.5±6.1	4.3±5.7	0.74
Duration of RRT (days)	0.48±2.28	0.39±2.0	0.41

Finfer S, et al. N Engl J Med 2004; 350: 2247-2256

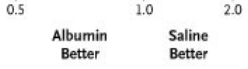
Comparison of Albumin versus Saline: The SAFE Study



Finfer S, et al. N Engl J Med 2004; 350: 2247-2256

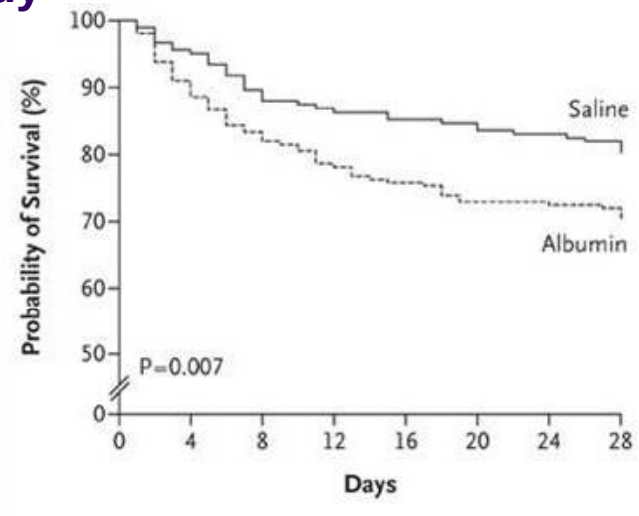
Comparison of Albumin versus Saline: The SAFE Study

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)



Finfer S, et al. N Engl J Med 2004; 350: 2247-2256

Albumin Resuscitation in TBI: *Post Hoc* Analysis of the SAFE Study



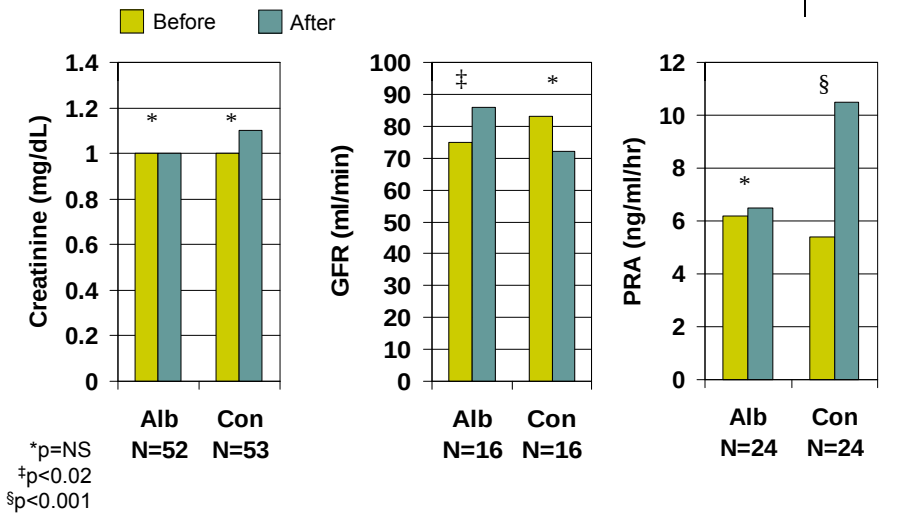
Myburgh J, et al. N Engl J Med 2007; 357: 874-884

Albumin Infusion in SBP

	Cefotaxime with Albumin (n=63)	Cefotaxime without Albumin (N=63)	*P*-value
Resolution of Infection	94%	98%	0.36
AKI	33%	10%	0.002
Mortality			
In-hospital	29%	10%	0.01
3 month	41%	22%	0.03

Sort P, et al. N Engl J Med 1999; 341: 403-409

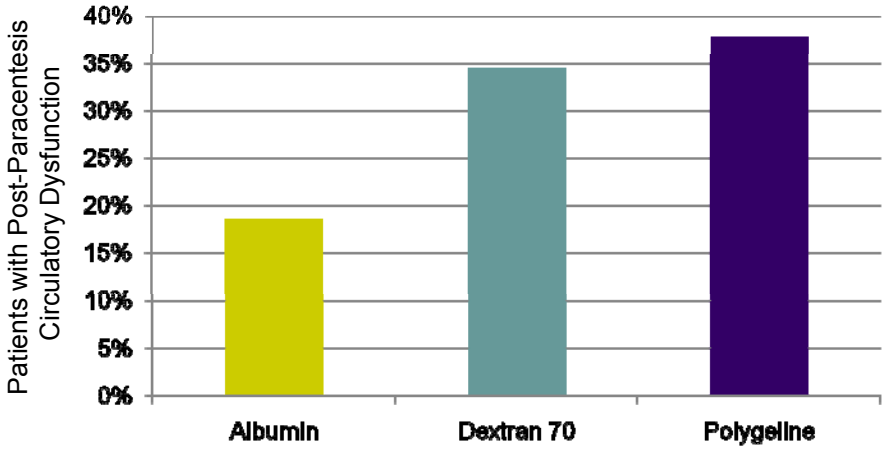
Intravenous Albumin after Large-Volume Paracentesis



*p=NS
‡p<0.02
§p<0.001

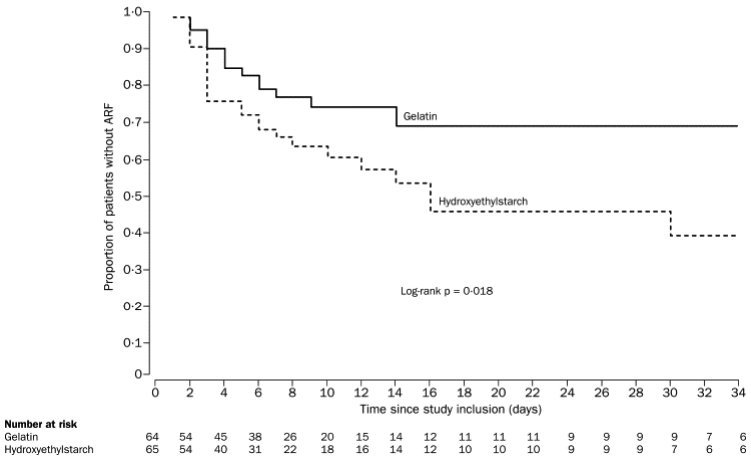
Gines P, et al. Gastro 1988; 94: 1493-1502

Post-Paracentesis AKI: Albumin, Dextran 70 or Polygeline



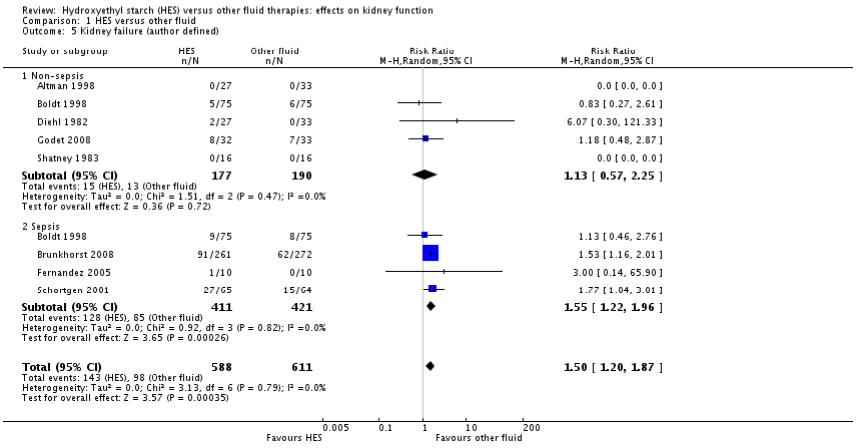
Gines P, et al. Gastro 1996; 111: 1002-1010

AKI Associated With Hydroxyethyl Starch versus Gelatin



Schortgen F, et al. Lancet 2001; 357: 911-916

AKI Associated With Hydroxyethyl Starch versus Other Fluids



Dart AB, et al. Cochane Database 2010: CD007594

Summary

- There is not a clearly defined window for fluid administration for prevention of AKI
- The volume that should be given is uncertain
  - Hemodynamic optimization reduces the risk for AKI
  - Excessive fluid administration may be harmful
- The optimal fluid composition is uncertain
  - It is unclear if there is a benefit to isotonic bicarbonate as compared to isotonic saline
  - There is no clear benefit to colloids
  - Hydroxyethyl starch is independently associated with increased risk of AKI