

A blurred background image of a hospital room. In the foreground, a nurse in green scrubs and a blue hairnet is seen from the side, working with medical equipment. In the background, there are several monitors displaying vital signs, a patient lying on a gurney, and other medical equipment. The overall scene is a busy clinical environment.

Journal Club 31.01.2013

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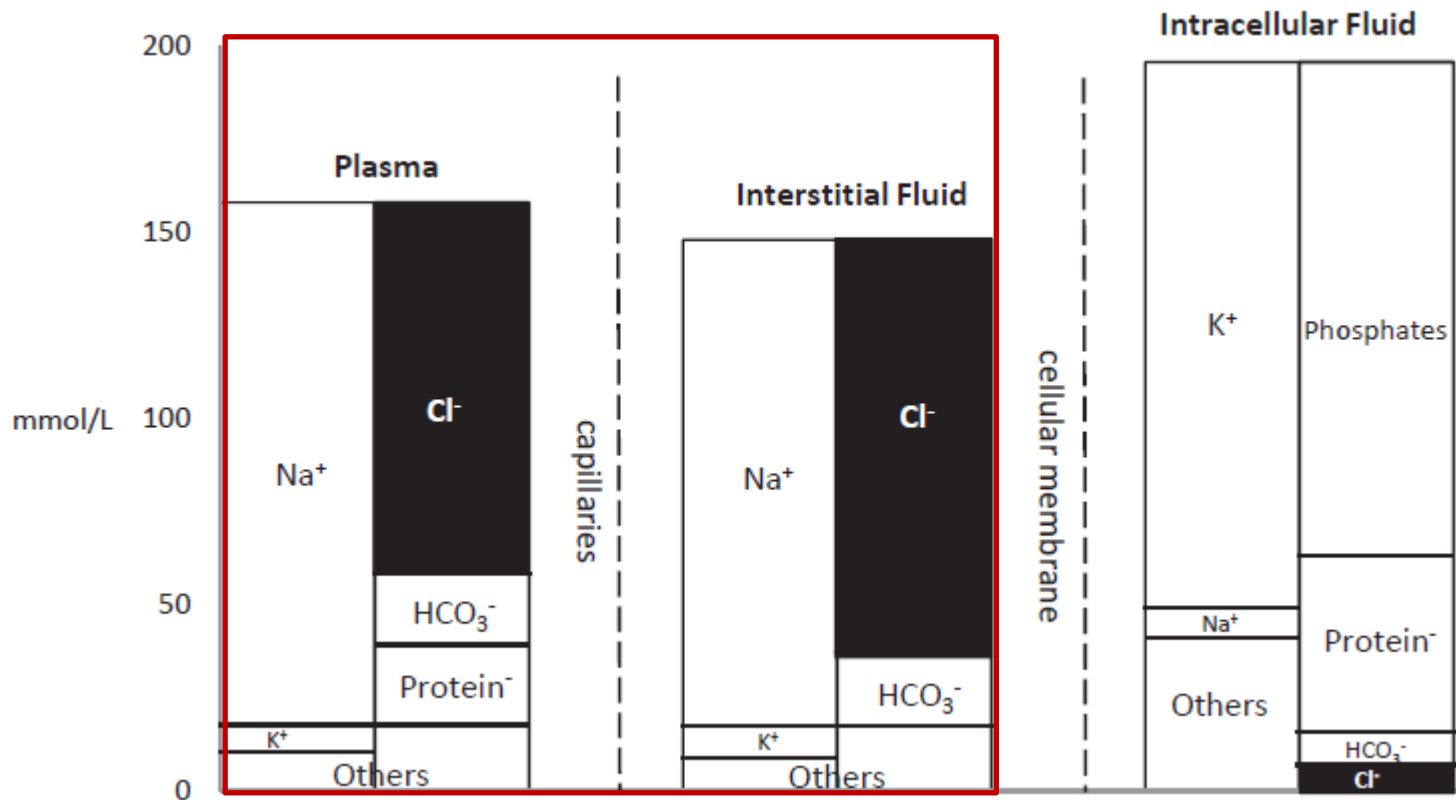
# Chloride: the forgotten electrolyte

JAMA 2012

# Background

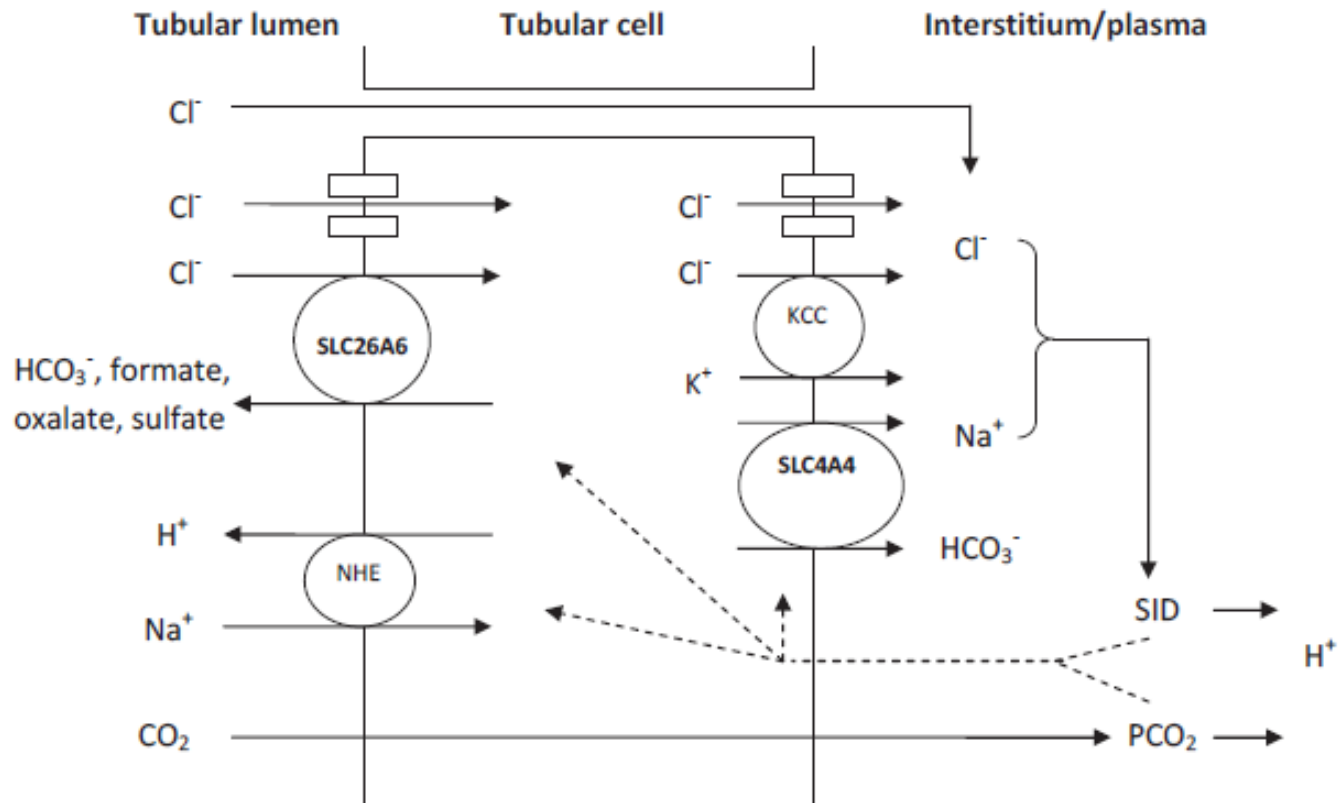
# Cl<sup>-</sup>

- Main source: dietary sodium chloride (= NaCl 0.9% 0.5-1.3l)
- Reference value 97-107mmol/l, but variation between assays



# Chloride

- 99.1% reabsorbed, mainly passive in the prox tubule



# Chloride



## In animals:

- Decreases short-time survival and acid-base balance
- Decreases systemic BP
- Pro-inflammatory
- Produces renal vasoconstriction and fall in GFR
- Increases renal vascular responsiveness to angiotensin II

## In adults:

- Decreased diuresis and natriuresis compared to lactate solution in healthy volunteers and patients undergoing surgery
- Decreased gastric mucosal perfusion post surgery in elderly
- Higher incidence of metabolic acidosis and hyperkalemia without effect on renal function in transplant
- Reduction of mean renal artery flow velocity and renal cortical tissue perfusion in healthy patient

## Cristalloids

	Concentration (mmol/l)				
	Plasma	0.9% NaCl	Hartmann's	Plasma-Lyte 148®	Sterofundin®
Sodium	140	154	131	140	140
Potassium	5	0	5	5	4
Chloride	100	154	111	98	127
Calcium	2.2	0	2	0	2.5
Magnesium	1	0	1	1.5	1
Bicarbonate	24	0	0	0	0
Lactate	1	0	29	0	0
Acetate	0	0	0	27	24
Gluconate	0	0	0	23	0
Maleate	0	0	0	0	5

## Colloids

	Concentration (mmol/l)					
	Plasma	Gelofusine®	Albumex®4	Voluven® (HES 6% 130/0.4)/ Venofundin® (HES 6% 130/0.42)	Hextend® (HES 6% 130/0.4)	Tetraspan® (HES 6% 130/0.42)
Sodium	140	154	140	154	143	140
Potassium	5	0	0	0	3	4.0
Chloride	100	125	128	154	124	118
Calcium	2.2	0	0	0	2.5	2.5
Magnesium	1	0	0	0	0.5	1.0
Bicarbonate	24	0	0	0	0	0
Lactate	1	0	0	0	28	0
Acetate	0	0	0	0	0	24
Malate	0	0	0	0	0	5
Octanoate	0	0	6.4	0	0	0

# Differences between iv fluid in AKI?

## ✓ Increased incidence of AKI with HES compared to gelatin

Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Schortgen F et al. Lancet 2001



## ✓ Similar outcome (mortality, days RRT) using albumin 4% versus saline.

A comparison of albumin and saline for fluid resuscitation in the intensive care unit. Finfer R. NEJM 2004.



## ✓ Hyperoncotic colloids and albumin are associated with ↑ AKI.

The risk associated with hyperoncotic colloids in patients with shock. Schortgen F. Int Care Med 2008



## ✓ Meta-analysis: gelatin compared to starches solution: less AKI.

Benefits and risks of using gelatin solution as a plasma expander for peri-operative and critically ill patients: a meta-analysis. Saw M. Anesth Int Care 2012



## ✓ Hyperoncotic albumin decreases AKI and hyperoncotic HES increased.

Hyperoncotic colloids and acute kidney injury: a meta-analysis. Wiedermann Cj. Crit Care 2010.

## ✓ Increased risk of death and RRT in HES treated septic patients..

Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. Perner A. NEJM 2012



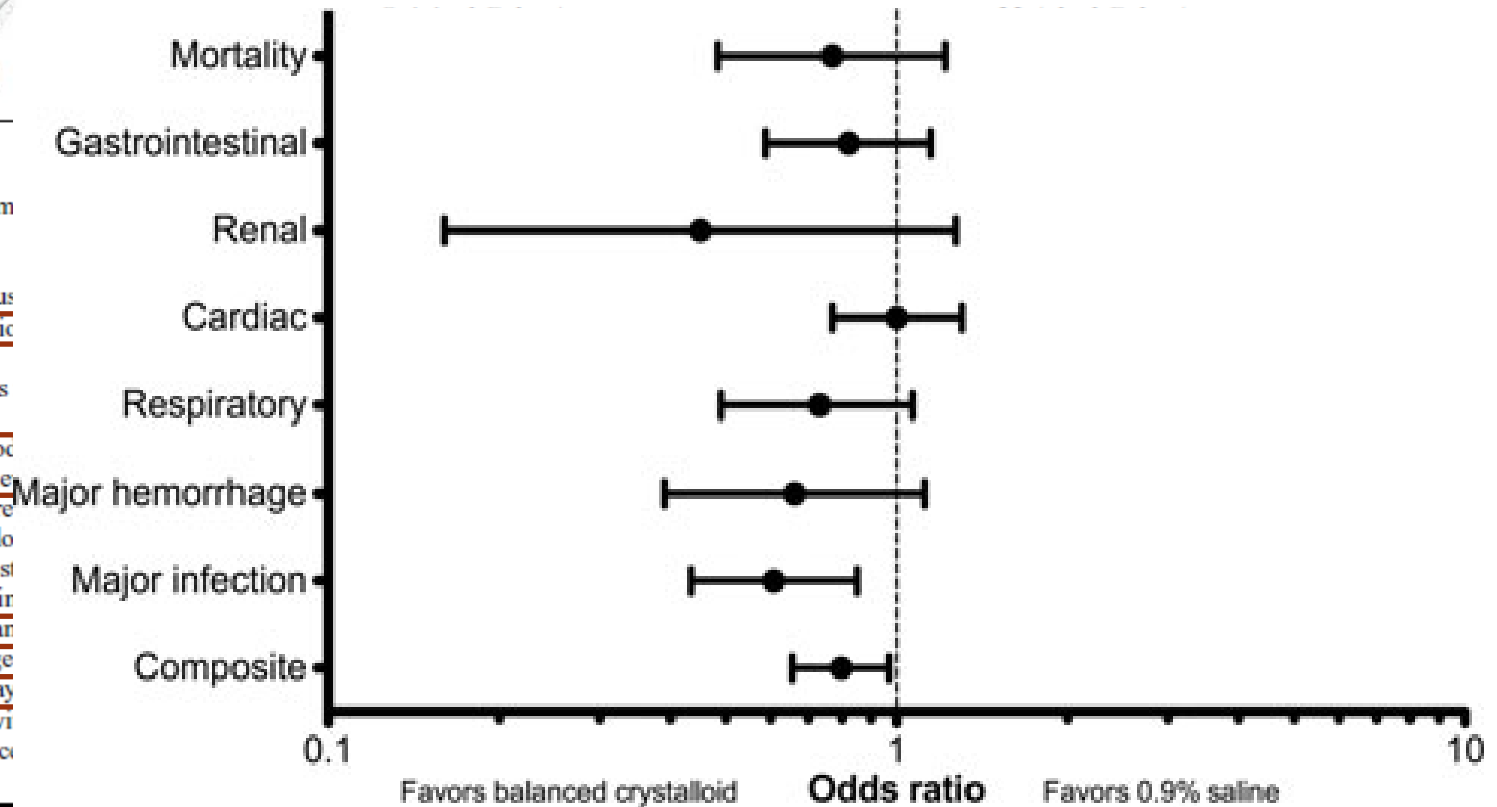
# Major Complications, Mortality, and Resource Utilization After Open Abdominal Surgery

*0.9% Saline Compared to Plasma-Lyte*

Shaw. Ann Surg 2012



- Medication
- Albumin
- Antinausea m
- Buffers
- Diuretics
- Crystalloid us
- Blood transfusio**
- Yes
- Median units
- Extra tests
- Arterial blood**
- Lactic acid le**
- Blood culture
- CT scan abdo
- CT scan chest
- CT scan brain
- LOS days, mean**
- Ventilator usage
- Ventilator day**
- Readmission w/
- Additional proc
- Dialysis



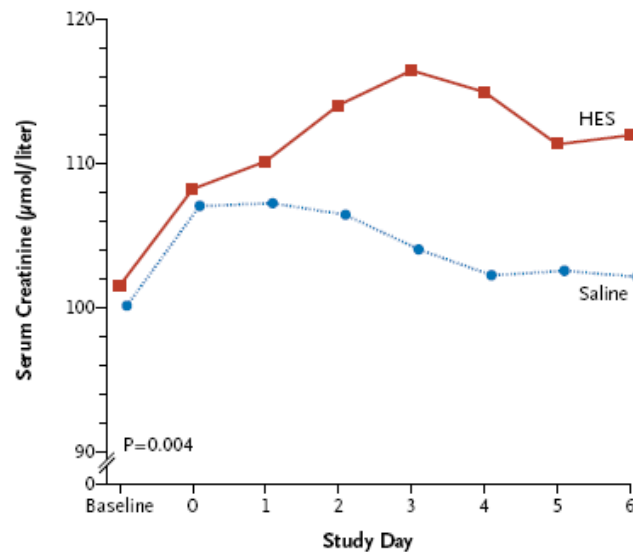
# Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care



John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D.,

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy.

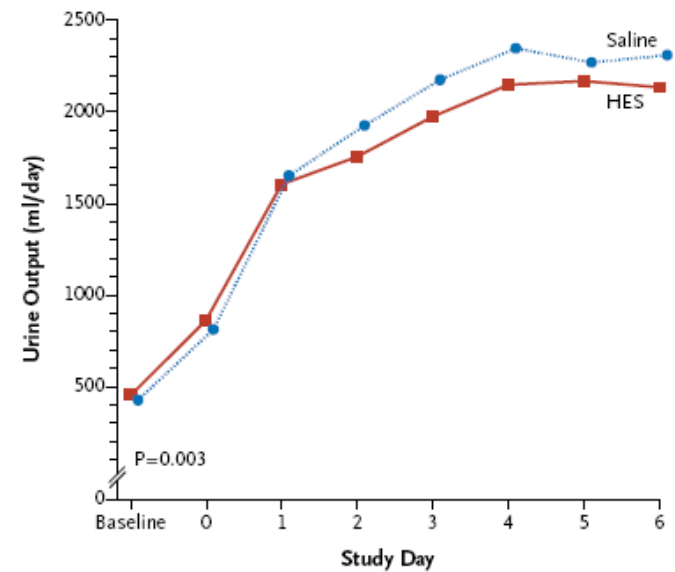
**A Serum Creatinine**



**No. at Risk**

	Baseline	0	1	2	3	4	5	6
HES	3260	2197	2899	2111	1576	1238	998	851
Saline	3283	2253	2916	2196	1614	1291	1026	857

**B Urine Output**



**No. at Risk**

	Baseline	0	1	2	3	4	5	6
HES	1417	3202	3076	2269	1702	1292	1071	894
Saline	1385	3237	3119	2341	1719	1348	1110	894

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

JAMA 2012



- ✓ Hypothesis: Chloride fluid restriction decreases incidence + severity of AKI

Outcome measures:

- I. Increase in creatinine (baseline-peak) according to RIFLE
- II. Need RRT, length of stay and survival

# Method

- ✓ Prospective, open-label (not randomised not blinded)
- ✓ multicentric study in 22 ICUs Australia
  - control phase 6 months 2008:  
*free to use any iv fluid*
  - wash-out period 6 months:  
*education period ICU, ER, OR*
  - intervention phase 6 months 2009:  
*saline 0.9% gelofusin, albumin 4% only if attending ok*
- ✓ All admissions. No exclusion criteria
- ✓ Statistics: GEEs (creat)
  - Logistic regression (AKI, RRT)
  - Kaplan-Meier, Cox regression (time to event)

# Fluids

High Chloride

Low Chloride



**Table 2.** Composition of Trial Fluids<sup>a</sup>

	0.9% Saline	Hartmann	4% Gelatin	Plasma- Lyte 148	Albumin	
					4%	20%
Sodium	150	129	154	140	140	48-100
Potassium	0	5	0	5	0	0
Chloride	150	109	120	98	128	19
Calcium	0	2	0	0	0	0
Magnesium	0	0	0	1.5	0	0
Lactate	0	29	0	0	0	0
Acetate	0	0	0	27	0	0
Gluconate	0	0	0	23	0	0
Octanoate	0	0	0	0	6.4	32

<sup>a</sup>All concentrations in mmol/L.

# Results

**Table 1.** Baseline Characteristics of the Patients During the Control and Intervention Periods

Follow-up: 11d	No. (%) [95% CI] of Patients <sup>a</sup>		P Value
	Control Period (n = 760)	Intervention Period (n = 773)	
Male sex	461 (61) [57-64]	483 (62) [59-66]	.46
Mechanical ventilation	498 (66) [62-69]	517 (67) [63-70]	.57
Admission after elective surgery	224 (29) [22-33]	232 (30) [27-33]	.82
Postoperative admission	377 (50) [46-53]	382 (49) [46-53]	.94
Admission from			
Emergency department	178 (23) [20-26]	168 (22) [19-25]	.43
Ward	129 (17) [14-20]	129 (17) [14-19]	.88
Admission for other ICU	76 (10) [8-12]	94 (12) [10-15]	.18
Diagnosis <sup>b</sup>			
Cardiovascular	294 (39) [35-42]	281 (36) [33-40]	.35
Gastrointestinal	126 (17) [14-19]	126 (16) [14-19]	.88
*Metabolic	53 (7) [5.1-8.8]	34 (4.4) [2.9-5.9]	.03
Neurological	47 (6.2) [4.4-7.9]	68 (8.8) [6.8-11.0]	.05
Renal or genitourinary	26 (3.4) [2.1-4.7]	21 (2.7) [1.5-3.9]	.42
Respiratory	107 (14) [12-17]	111 (14) [12-17]	.87
Comorbidities <sup>b</sup>			
Severe sepsis or septic shock	55 (7.2) [5.4-9.0]	75 (10.0) [7.6-12.0]	.08
Chronic lung disease	18 (2.4) [1.3-3.5]	15 (1.9) [0.9-2.9]	.56
Chronic cardiovascular disease	19 (2.5) [1.4-3.6]	32 (4.1) [2.7-5.6]	.07
	<b>Mean (95% CI)</b>		
Age, y	60 (59.0-61.6)	60.5 (59.2-61.8)	.86
APACHE II score (range: 0-71) <sup>c</sup>	15.8 (15.2-16.4)	16.0 (15.4-16.6)	.63
APACHE III score (range: 0-300) <sup>c</sup>	58 (56-60)	58 (56-60)	>.99
SAPS II (range: 0-163) <sup>c</sup>	32.4 (31.2-33.6)	32.4 (31.2-33.6)	.94
Baseline creatinine level, $\mu\text{mol/L}$	90 (69-125)	86 (67-121)	.07

# Previous results

Yunos. Crit Care Med 2011

	Control (21,694 Measurements)	Intervention (19,807 Measurements)	<i>p</i>
Severe hypochloremia, chloride <90 mmol/L, no. (%)	205 (0.9%)	287 (1.4%)	<.001
Severe hyperchloremia chloride >114 mmol/L, no. (%)	1,353 (6.2%)	465 (2.3%)	<.001
Severe dyschloremia, no. (%)	1,558 (7.2%)	752 (3.7%)	<.001
Severe hyponatremia, sodium <127 mmol/L, no. (%)	543 (2.5%)	543 (2.7%)	.129
Severe hypernatremia, sodium >156 mmol/L, no. (%)	205 (0.9%)	31 (0.2%)	<.001
Severe dysnatremia, no. (%)	748 (3.4%)	574 (2.9%)	.001
Standard base excess <-5 mEq/ L, no. (%)	1,964 (9.1%)	1,185 (6.0%)	<.001
Standard base excess >5 mEq/L, no. (%)	5,500 (25.4%)	6,491 (32.8%)	<.001
Severe metabolic acid-base derangements, no. (%)	7,464 (34.4%)	7,676 (38.8%)	<.001
pH <7.3, no. (%)	1,309 (6.0%)	973 (4.9%)	<.001
pH >7.5, no. (%)	2,275 (10.5%)	2,909 (14.7%)	<.001
Severe pH derangements, no. (%)	3,584 (16.5%)	3,882 (19.6%)	<.001

# Previous results

Yunos. Crit Care Med 2011

	Control Group (n = 100)	Intervention Group (n = 100)	<i>p</i>
0.9% saline, mL	695 (165–1681)	0 (0–0)	<.001
Succinylated gelatin (Gelofusine), mL	50 (0–825)	0 (0–0)	<.001
Albumin 4% in sodium chloride (Albumex 4), mL	0 (0–275) (405) <sup>a</sup>	0 (0–0) (44) <sup>a</sup>	<.001
Hartmann's solution, mL	0 (0–0)	1840 (770–3611)	<.001
Plasma-Lyte 148, mL	0 (0–0) (41) <sup>a</sup>	0 (0–0) (205) <sup>a</sup>	<.01
Albumin 20% (Albumex 20), mL	0 (0–100)	200 (0–300)	<.001
Total intravenous fluids intake, mL	2277 (885–3916)	2590 (980–5185)	.62
Total urine output, mL	5163 (2743–8051)	4215 (2130–6723)	.323



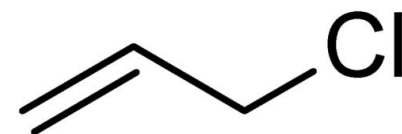
	Control, U.S. \$	Intervention U.S. \$
0.9% saline	2,680	58
Succinylated gelatin (Gelofusine)	11,755	0
Hartmann's solution	522	3,563
Plasma-Lyte 148	118	295
Total	15,077	3,915

# Fluids



Prescriptions	Control (n=760)	Intervention (n=773)	p
<b>Saline 0.9% I</b>	2411	52	<0.001
<b>Gelatin 4%</b>	538	0	<0.001
<b>Albumin 4%</b>	269	80	<0.001
<b>Hartmann</b>	469	3205	<0.001
<b>Plasmalyte</b>	65	160	0.04
<b>Albumin 20%</b>	87	268	<0.001
<b>Chloride</b> mmol/patient	694	496	na
<b>Sodium</b> mmol/patient	750	623	na
<b>Potassium</b> mmol/patient	3.5	22	na
<b>Lactate</b> mmol/patient	18	120	na

# I. AKI incidence



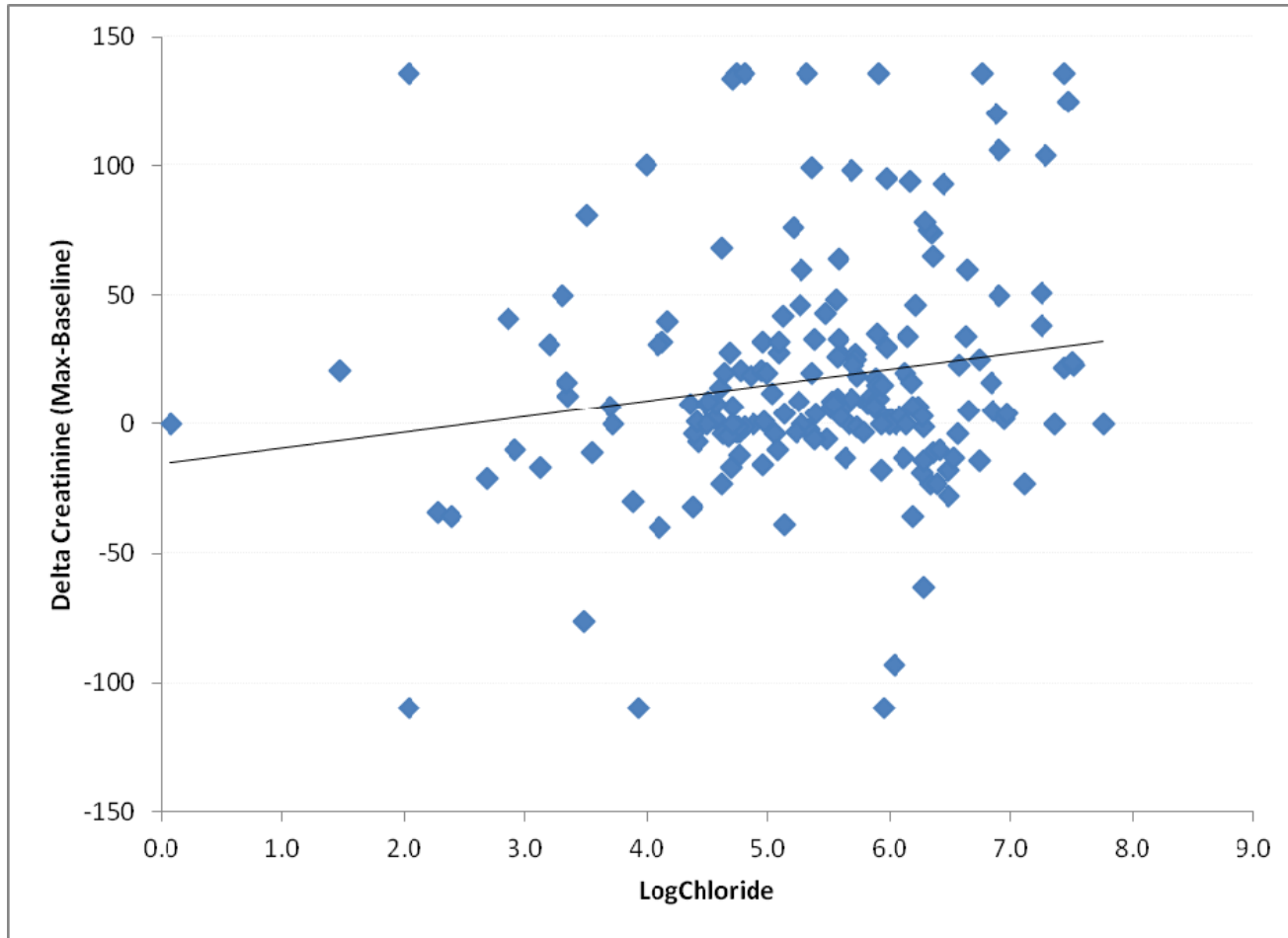
**Table 3.** Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

RIFLE class	No. (%) [95% CI] of Patients <sup>a</sup>		P Value
	Control Period (n = 760)	Intervention Period (n = 773)	
Risk	71 (9.0) [7.2-11.0]	57 (7.4) [5.5-9.0]	.16
Injury	48 (6.3) [4.5-8.1]	23 (3.0) [1.8-4.2]	.002
Failure	57 (7.5) [5.6-9.0]	42 (5.4) [3.8-7.1]	.10
Injury and failure	105 (14) [11-16]	65 (8.4) [6.4-10.0]	<.001

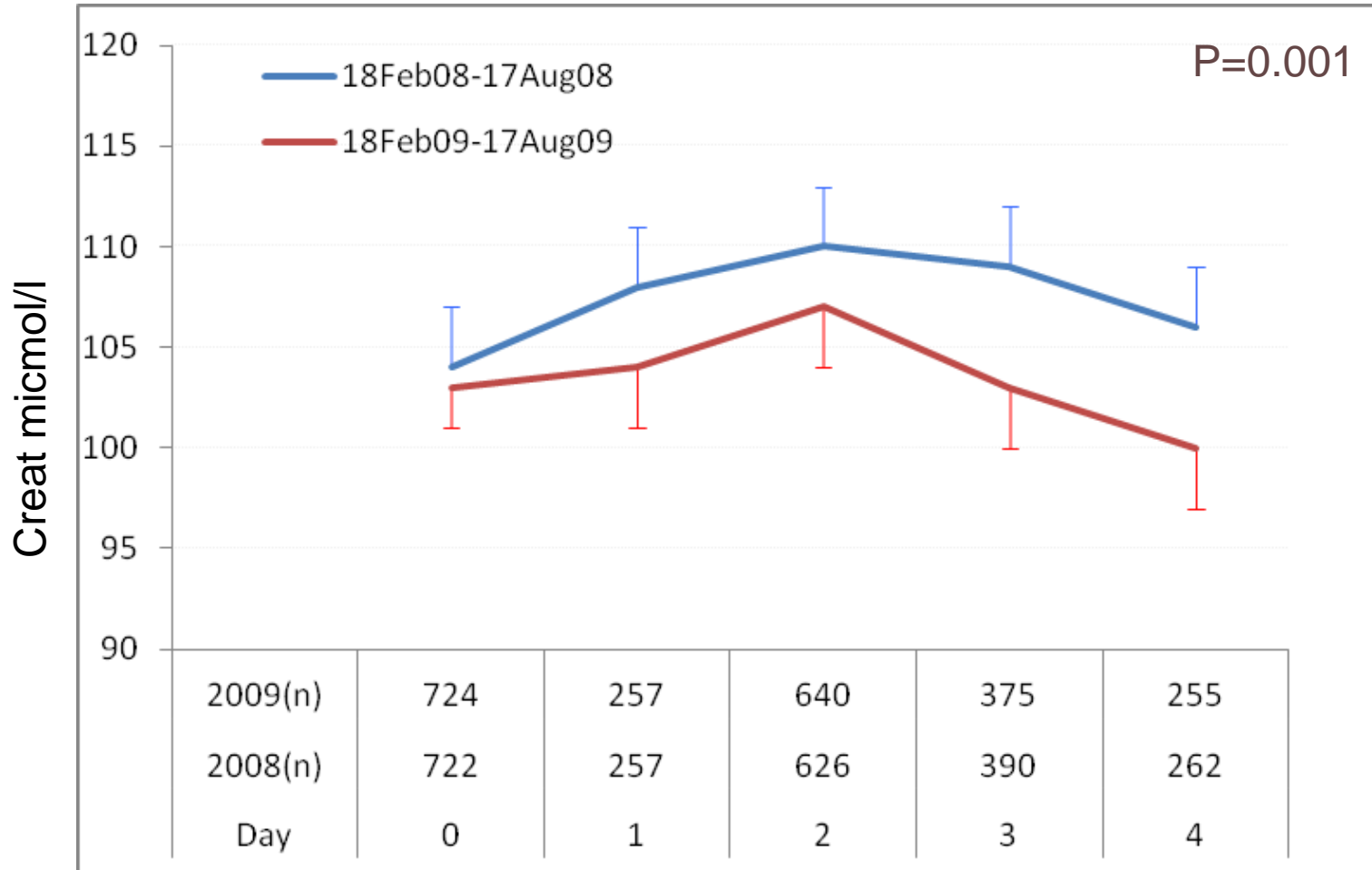
<sup>a</sup>The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.

<b>Decrease in creatinine</b> micromol/l	14.8 [9.8-19.9]	22.6 [17.5-27.7]	0.03
<b>RRT need n (%)</b>	78 (10) [8.1-12]	49 (6.3) [4.6-8.1]	0.005

## Relation between increased creatinine and chloride

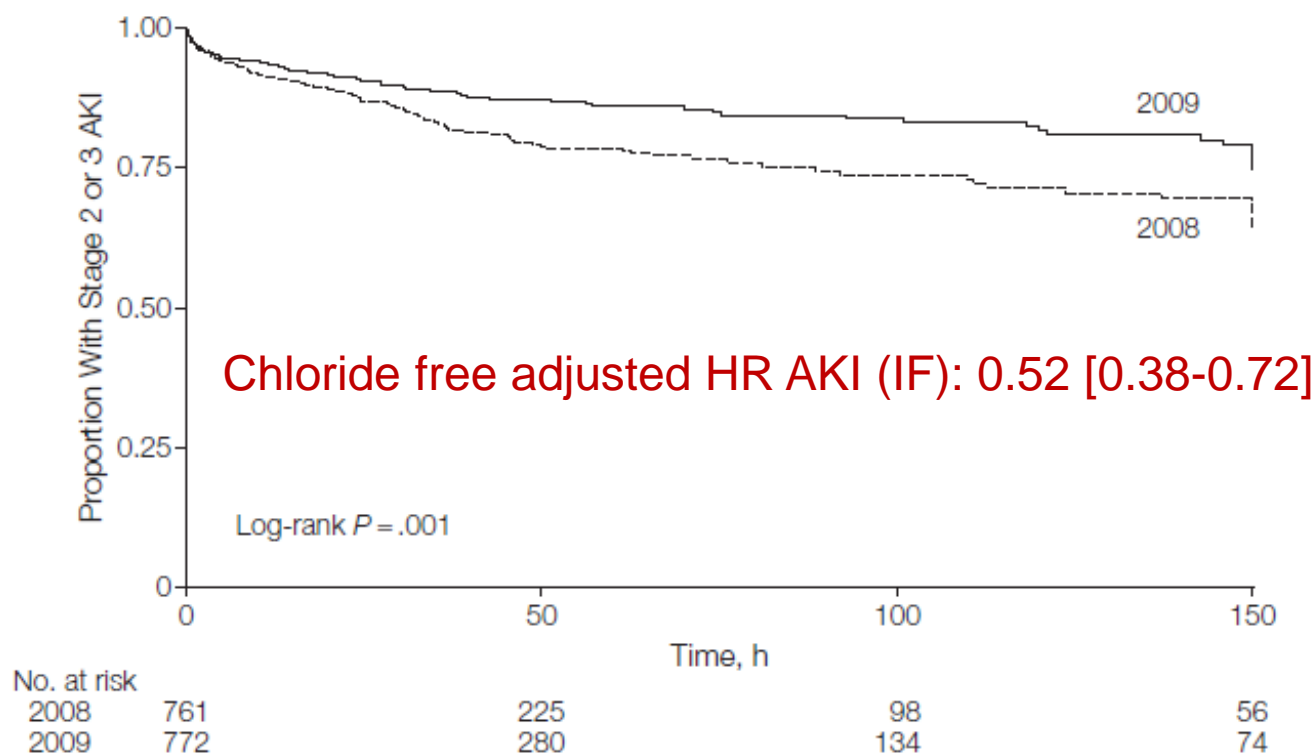


- I. Chloride free adjusted OR AKI (IF): 0.52 [0.37-0.75]
- II. Chloride free adjusted OR RRT: 0.52 [0.33-0.81]



# I. Time to AKI

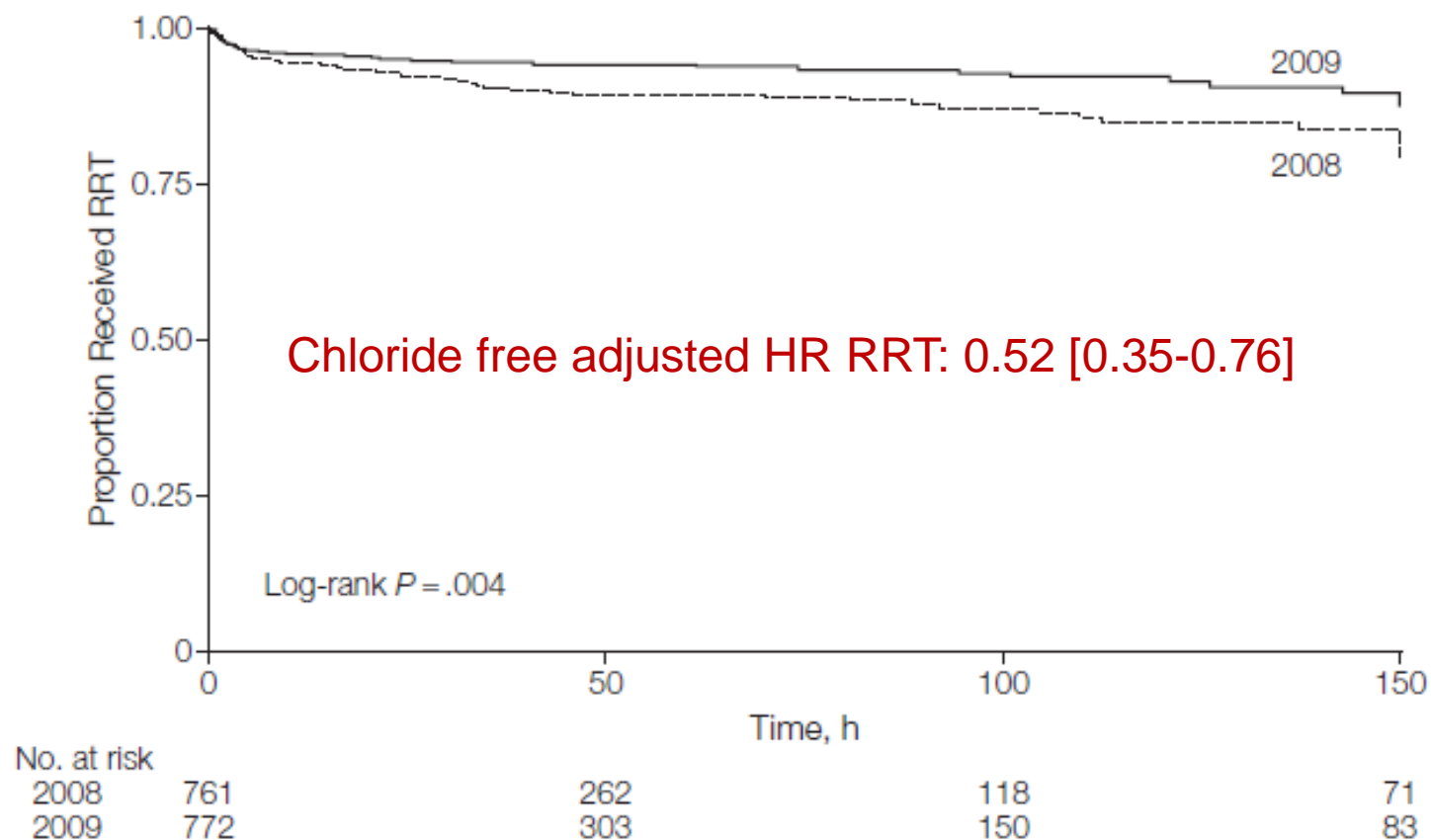
**Figure 1.** Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)



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

## II. Time to RRT

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



## II. Post hoc analysis

- ICU Mortality: no difference ( $_c65$  vs  $_i59$ )
- Hospital mortality: no difference ( $_c112$  vs  $_i102$ )
- ICU stay: no difference ( $_c42.9$  vs  $_i42.8h$ )
- Hospital stay: no difference ( $_c11d$  vs  $_i11d$ )
- RRT at 3 months: no difference ( $_c6$  vs  $_i5$ )

# Conclusions - discussion

Chloride-fluid restriction:

- Reduces creatinine increase
- Decreases AKI and RRT
- Increases time to AKI and RRT

BUT

- Not randomised not controlled but multicentric
- Different period time but no other changes
- 6 different types of fluids
- Chloride or salt effect?

