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G15 Fluids and Solutions in the Critically Ill 2: Solutions for CRRT

Sean M Bagshaw, MD, MSc
Division of Critical Care Medicine
University of Alberta

Alberta Health Services

AHFMR
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

Alberta Innovates Health Solutions

Disclosure

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- **Consulting:**
  - Alere, Baxter, Gambro, Spectral Diagnostics, Otsuka
- **Speaking:**
  - Alere, Gambro, Otsuka

Objectives

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- Selection of **BASE BUFFER**
- Replacement of **NUTRIENTS**
- Replacement of **ELECTROLYTES**
- **SAFETY** of Substitution Fluids
- Management of **DYSNATREMIAS**
- Types of commercial **SOLUTIONS**

CRRT Fluid Volume

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Dose* (mL/kg/hr)	Fluid (mL/hr)	Fluid (L/day)
15	1200	28.8
20	1600	38.4
25	2000	48.0
30	2400	57.6
35	2800	67.2
40	3200	76.8

* 80 kg patient ~ TBW 48 L

Plasma/CRRT Fluid Composition

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Parameter	[Plasma] (mmol/L)	CRRT [Fluid] (mmol/L)
[Na+]	135-145	136-145
[K+]	3.5-5.0	0-4.0
[Mg++]	0.7-1.0	0.5-1.5
[Ca++]	1.0-1.6	0-1.5
[Cl-]	100-108	106-120
[Lac-]	0.5-2.0	3-45
[HCO3-]	22-26	22-32
[Gluc]	4.5-6.1	0-5.5
Osm	280-296	282-300
[SID]	+40	+35-40

Selection of Base Buffer

- **Bicarbonate** ~ current standard
  - Historically not available due to instability + risk of contamination
- **Lactate**
- **Citrate**
- **Acetate**

Selection of Base Buffer (Lactate)

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- Metabolized to HCO3 by liver
- Utilized as energy substrate ~ PYR (CAC) or glucose
- Healthy person metabolize ~ 1500 mmol/day
  - [Lac] buffered fluids ~ 40-45 mmol/L
  - Patients receive 80-135 mmol/hr (1920-3240 mmol/day)
- Probably similar safety/efficacy to correct acidosis
- ↑ [Lac-] may contribute to clinical uncertainty
- Toxicity with reduced clearance (shock states)
  - Impaired myocardial contractility/hemodynamic instability
  - Metabolic acidosis

The acid-base effects of continuous hemofiltration with lactate or bicarbonate buffered replacement fluids

H.K. TAN, S. UCHINO, R. BELLOMO

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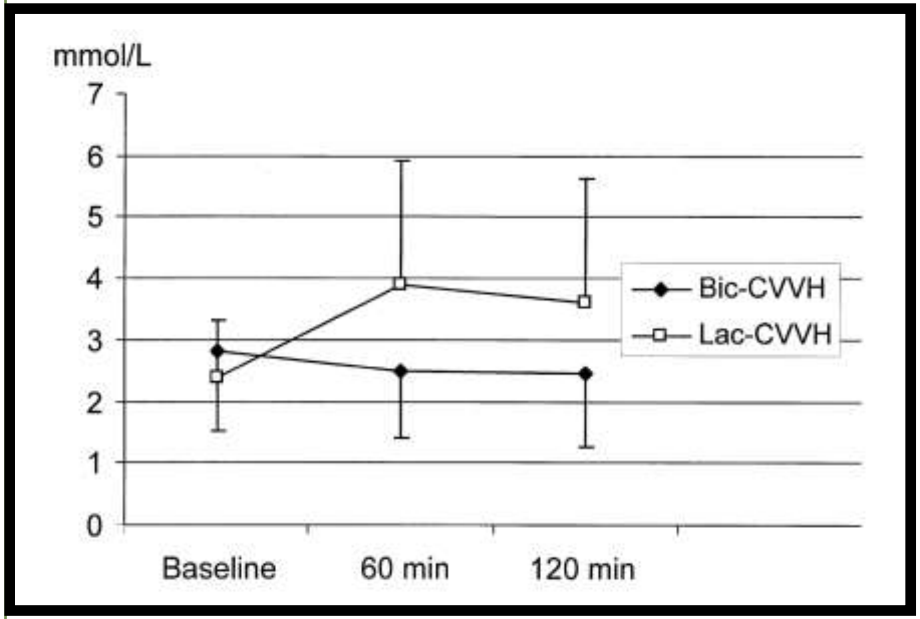
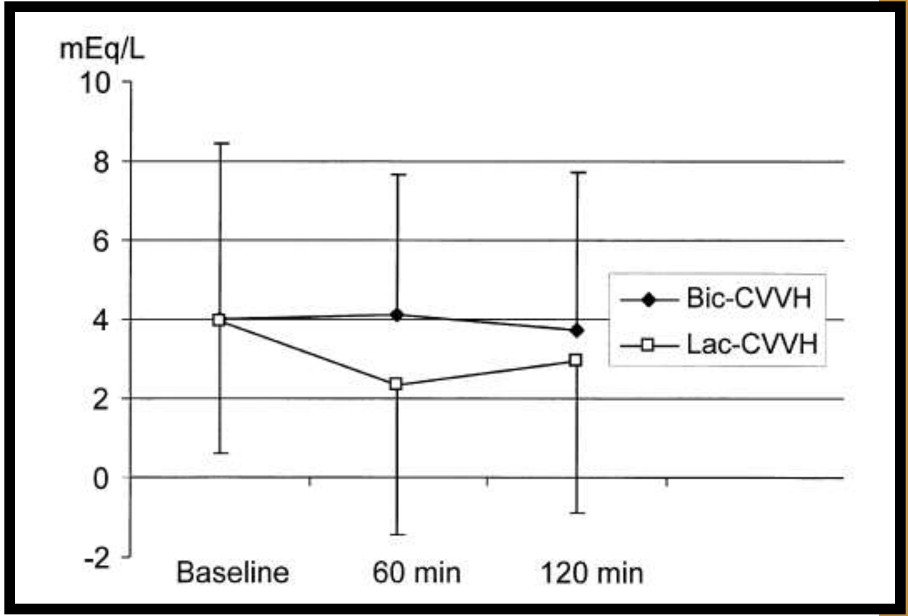


Serum Lactate



Base Excess

Tan et al IJAO 2003

Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients

MICHAEL BARENBROCK, MARTIN HAUSBERG, FRITZ MATZKIES, STEPHAN DE LA MOTTE, and ROLAND M. SCHAEFER

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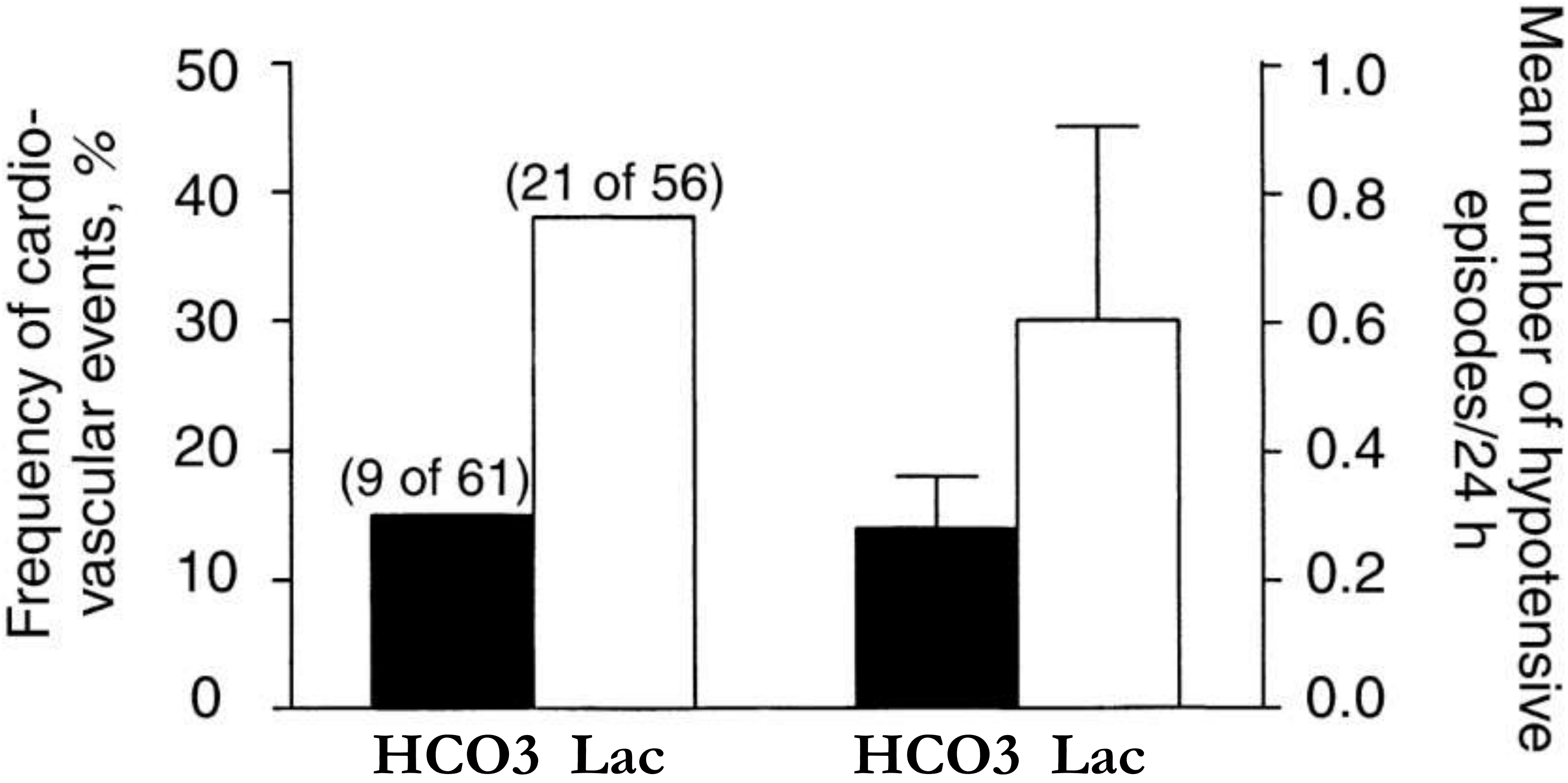

Barenbrock et al KI 2000

Selection of Base Buffer (Citrate)

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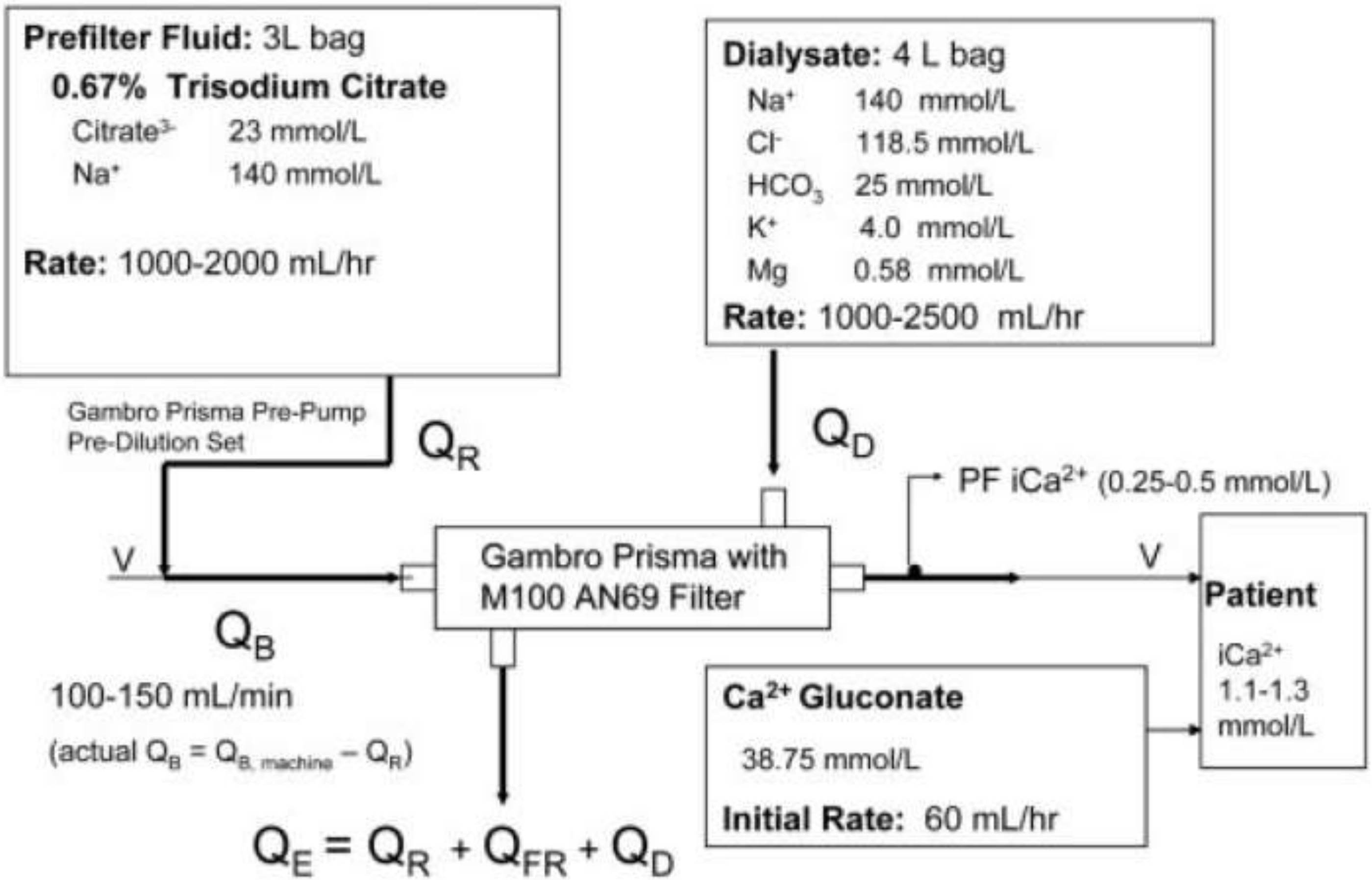
- Regional anticoagulant AND buffer
  - Chelates Ca++
- Metabolized (1:3) to HCO3 by liver, muscle, kidney
  - Impaired in liver failure/shock states
- Risk of citrate toxicity ~
  - Systemic ↓ ionized Ca++
  - Dysnatremia/metabolic alkalosis/acidosis
    - May be exacerbated in massive transfusion

A Practical Citrate Anticoagulation Continuous Venovenous Hemodiafiltration Protocol for Metabolic Control and High Solute Clearance

Ashita J. Tolwani, Mary B. Prendergast, Rajesh R. Speer, Brenda S. Stofan, and Keith M. Wille



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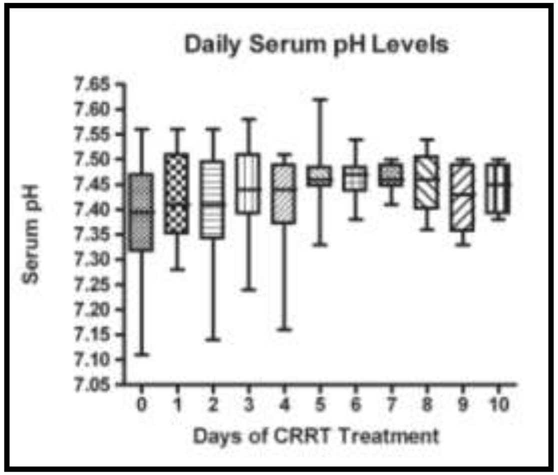
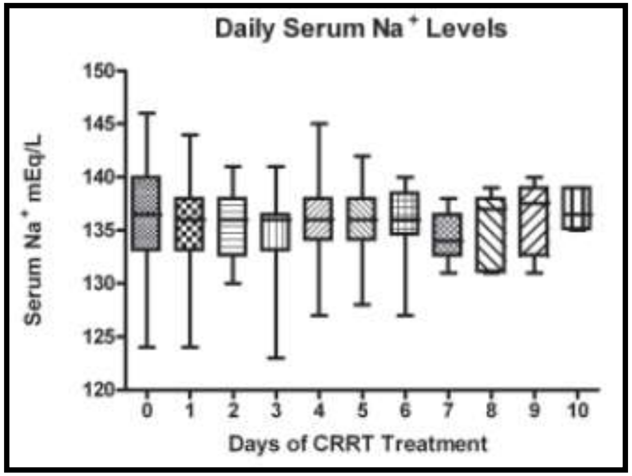
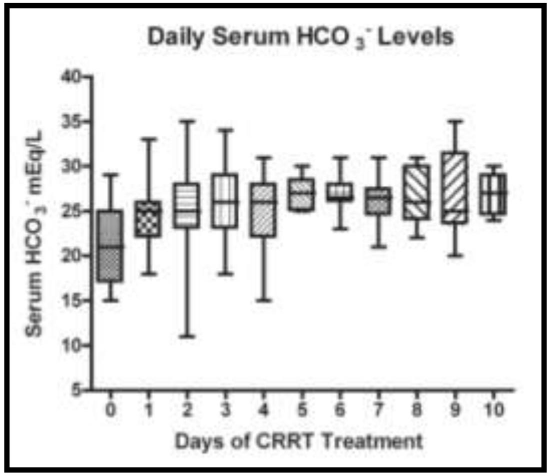
Serum pH



Serum Na+



Serum HCO3



Simplified dilute RCA (0.5%, 0.67%) protocol ~ can sustain effective clearance, metabolic control, hemofilter patency, and reduce costs

Tolwani et al CJASN 2006

Selection of Base Buffer (Acetate)

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- Metabolized to HCO_3 in liver/skeletal muscle
- May be poorly metabolized in critical illness:
  - Accumulation → hemodynamic instability
- Data from IHD literature
  - Impaired myocardial performance
- Now rarely used

Comparison of a Lactate- Versus Acetate-Based Hemofiltration Replacement Fluid in Patients with Acute Renal Failure

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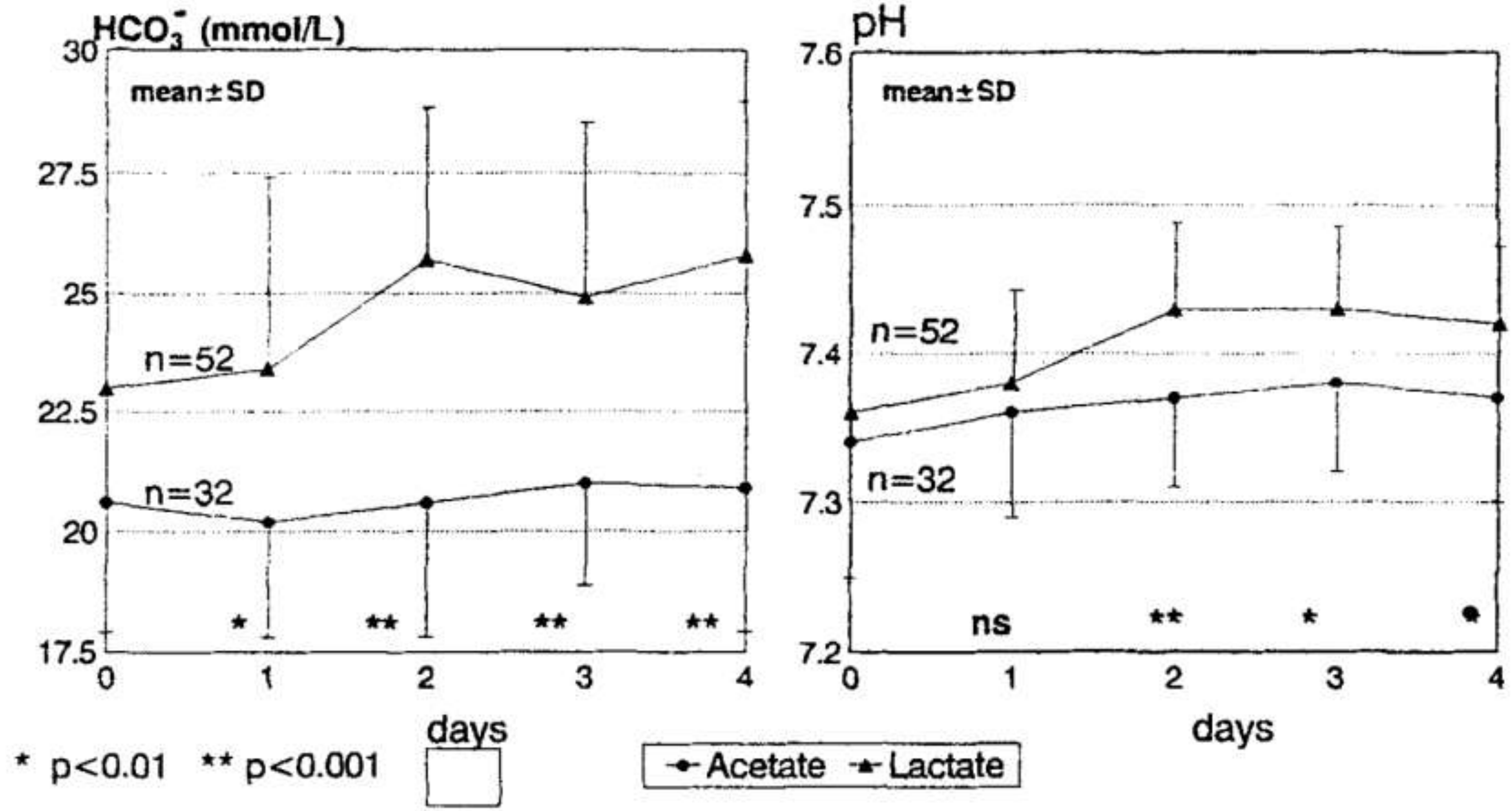

Morgera et al Ren Fail 1997

The use of different buffers during continuous hemofiltration in critically ill patients with acute renal failure

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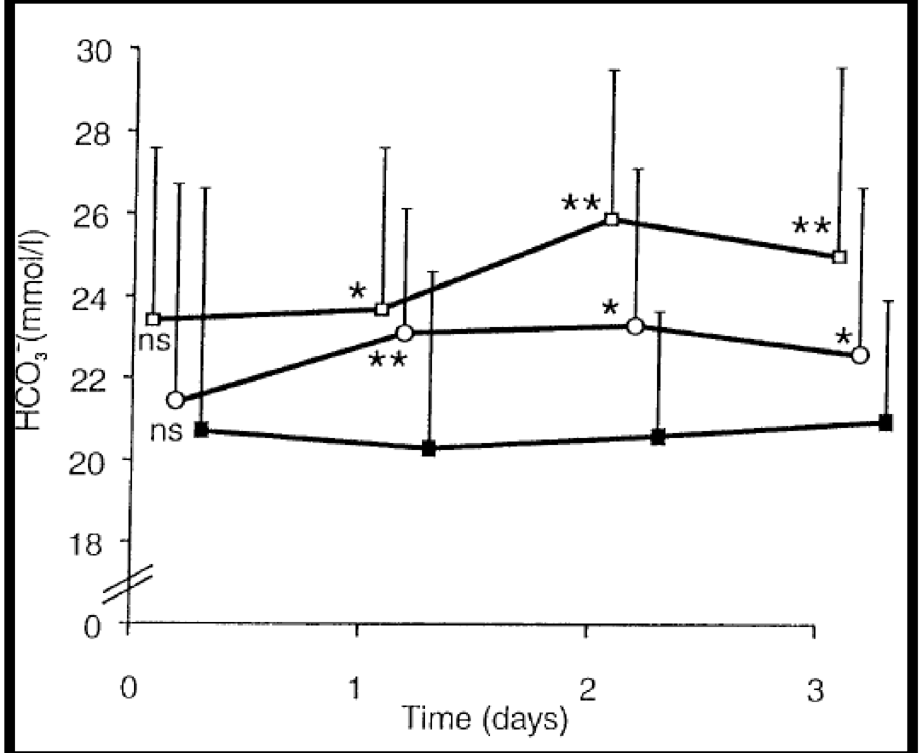

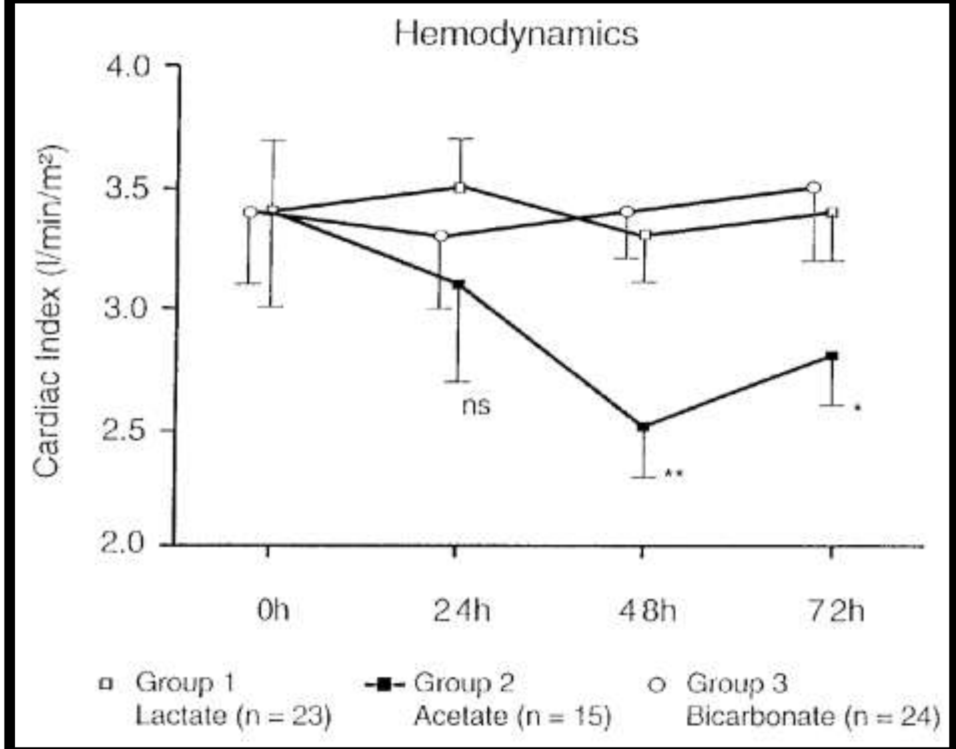

Heering et al ICM 1999

CRRT Fluids DO NOT Contain

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- **Micronutrients:**
  - Trace elements
  - Metals (water-soluble)
  - Vitamins (water-soluble)
  - Amino acids
  - Carnitine
  - Glucose (contained in some preparations)*

…are all lost during CRRT

GLUCOSE Loss in CRRT

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- GLUCOSE loss during CRRT can be significant:
- For fluid without glucose ~ UF ~ 2500 mL/hr
  - BG 100 mg/dl [5.5 mmol/l] loss 60g (250kcal/d)
  - BG 150 mg/dl [7.5 mmol/l] loss 90g (360kcal/d)
- GLUCOSE loss, in absence of compensatory losses, may exacerbate liver gluconeogenesis

Wiesen et al JPEN 2011

AMINO ACID Loss in CRRT

- Amino acids have small MW (~ 145 Da)
  - Sieving coefficient → 1.0
- Clearance will depend up:
  - Available circulating AA pool
  - Protein metabolism/turnover (Ra)
  - Filter-specific sieving-coefficient
  - UF rate, BFR, CRRT mode + duration

Intensive Care Med (2001) 27: 84–90
DOI 10.1007/s001340000703

ORIGINAL

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H.M. Oudemans-van Straaten
R.J. Bosman
M. Treskes
H.J.I. van der Spoel
D.F. Zandstra

Plasma glutamine depletion and patient outcome in acute ICU admissions

- **Glutamine** ~ Most abundant AA in body
  - Precursor for nucleotide biosynthesis in rapidly dividing cells (i.e. immune, gut)
  - Substrate in glutathione synthesis + renal NH3 genesis
- **Low glutamine** (<0.42 mmol/L) ~
  - Older age, illness severity, shock states
  - **Higher observed mortality** (60 vs. 29%, p<0.01)

Glutamine kinetics during intravenous glutamine supplementation in ICU patients on continuous renal replacement therapy

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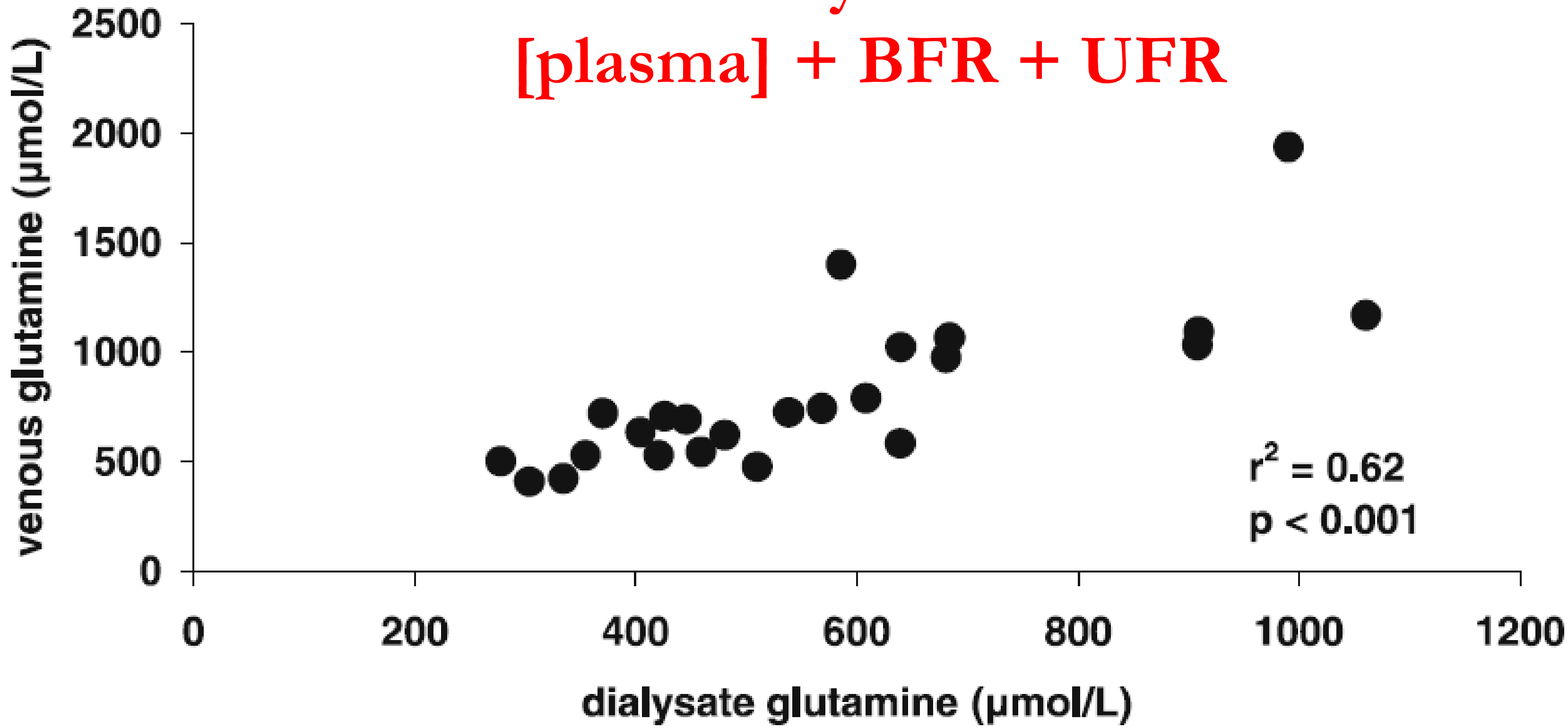
Glutamine in Dialysate correlated with [plasma] + BFR + UFR



Berg et al ICM 2007

Glutamine kinetics during intravenous glutamine supplementation in ICU patients on continuous renal replacement therapy

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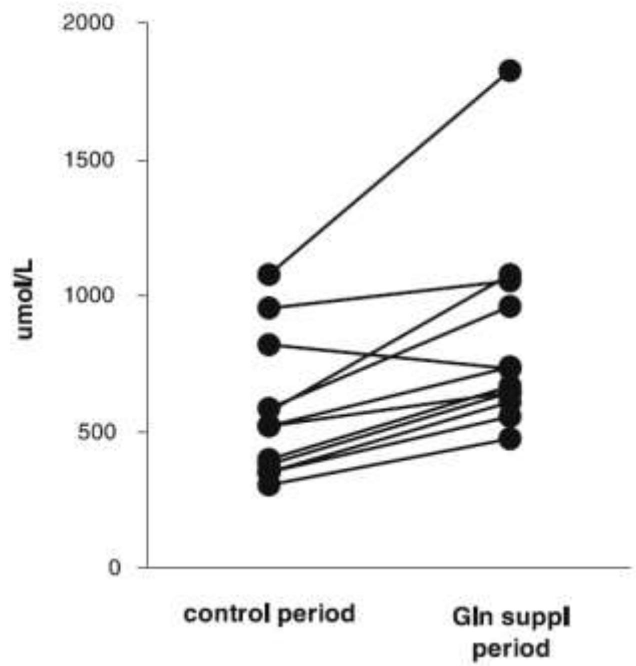
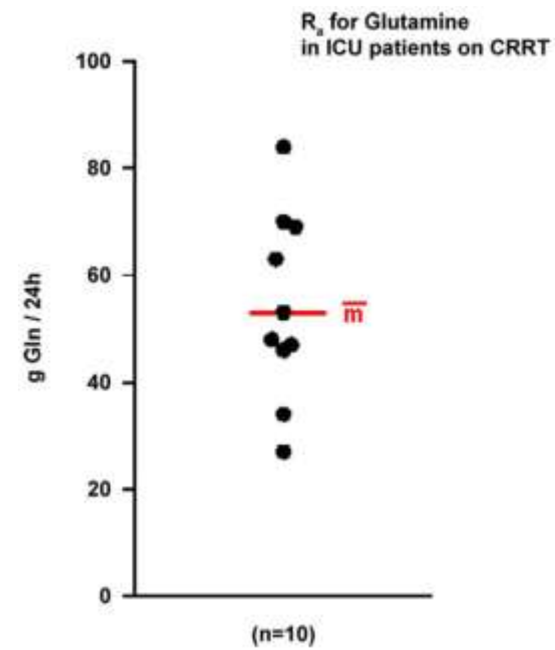
831 vs. 570 µmol/L, $p<0.01$ **Ra (turnover) ~ 54 g/day**





CRRT loss ranged 0.5-6.8 g/day → CL_{CRRT} ~ 5.3%

Glutamine loss, if not supplemented, is accelerated!

Berg et al ICM 2007

Serum concentrations and clearances of folic acid and pyridoxal-5′-phosphate during venovenous continuous renal replacement therapy

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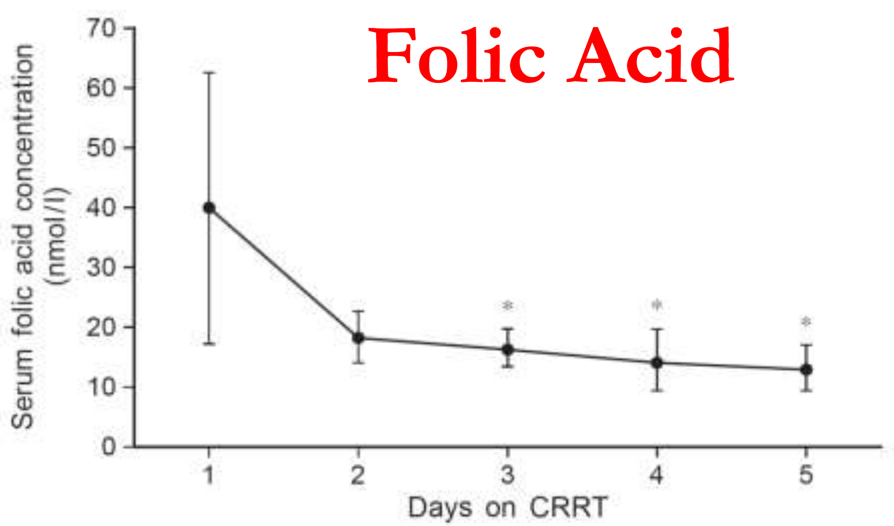

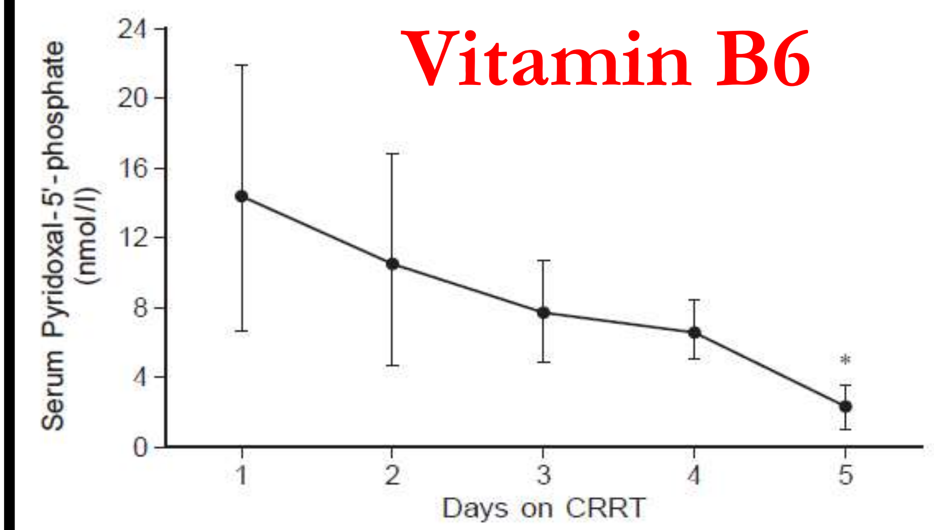

↓ 12.6% per day

↓ 13.7% per day

Fortin et al ICM 1999

Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients[1–3]

Mette M Berger, Alan Shenkin, Jean-Pierre Revelly, Eddie Roberts, M Christine Cayeux, Malcolm Baines, and Rene L Chioléro

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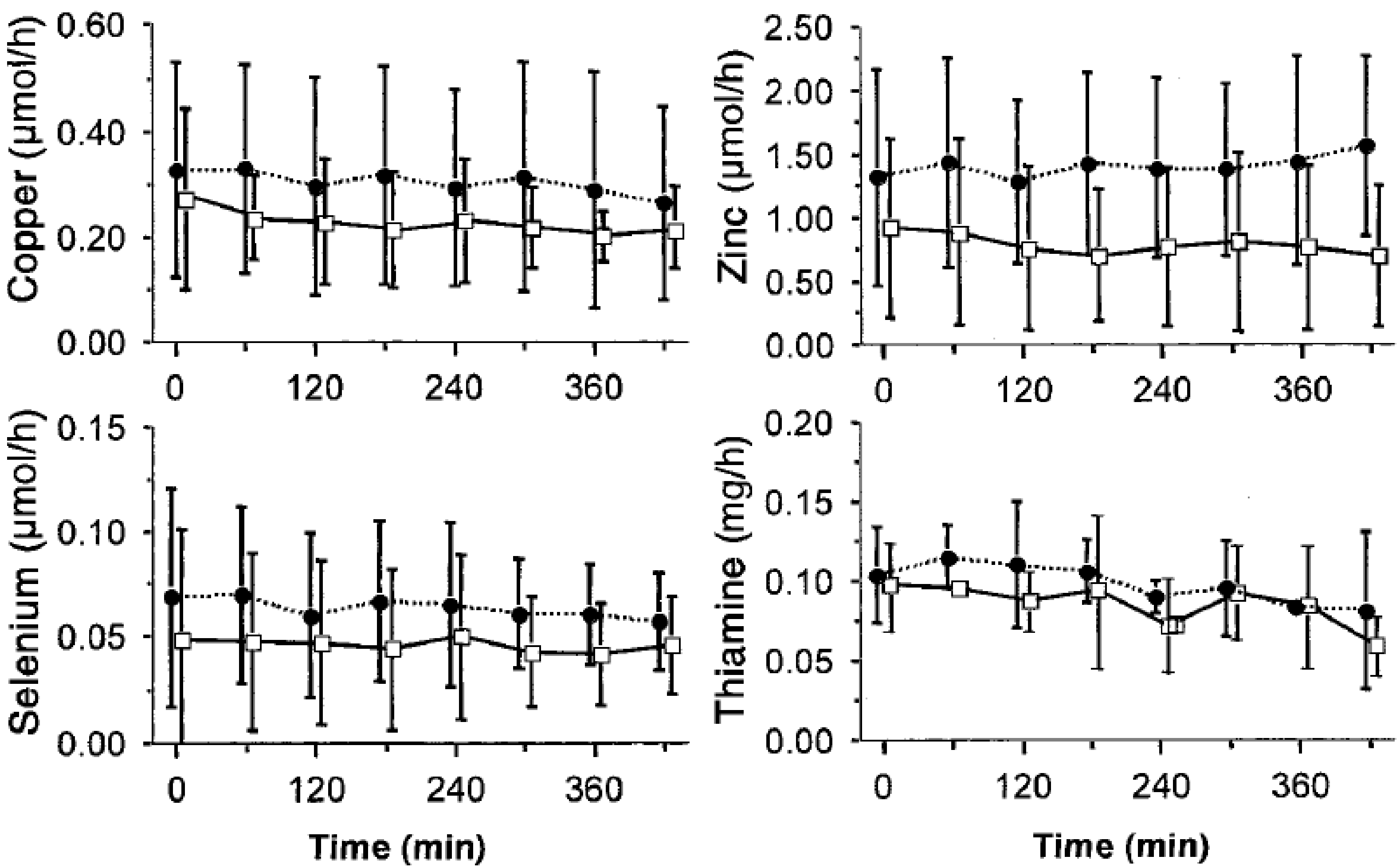

Berger et al Am J Clin Nutr 2004

Micronutrient Loss in CRRT

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Micronutrient	Impact of CRRT
Trace Elements	
Zinc	0 to ↑
Selenium	↓↓
Copper	↓↓
Chromium	↓↓
Manganese	↓↓
Iron	↓
Nickel	↑
Vitamins	
Folic acid (B9)	↓
Pyridoxal phosphate (B6)	↓
Thiamine	↓↓
Vitamin C	↓
Vitamin E	↓

Wiesen et al JPEN 2011

Hypophosphatemia during continuous hemodialysis is associated with prolonged respiratory failure in patients with acute kidney injury

Sevag Demirjian[1], Boon Wee Teo[2], Jorge A. Guzman[3], Robert J. Heyka[1], Emil P. Paganini[1], William H. Fissell[1], Jesse D. Schold[4] and Martin J. Schreiber[1]

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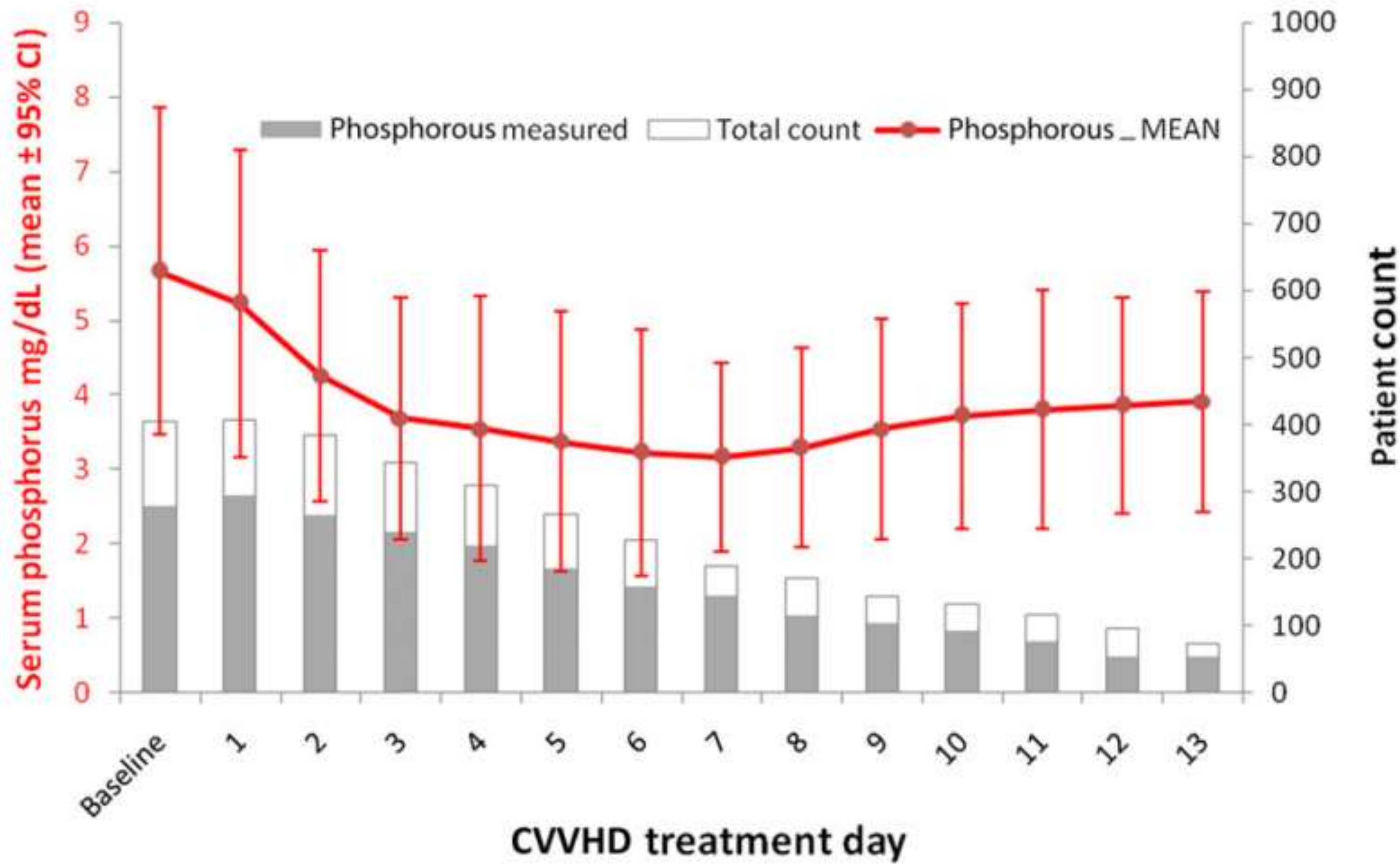

Demirjian et al NDT 2011

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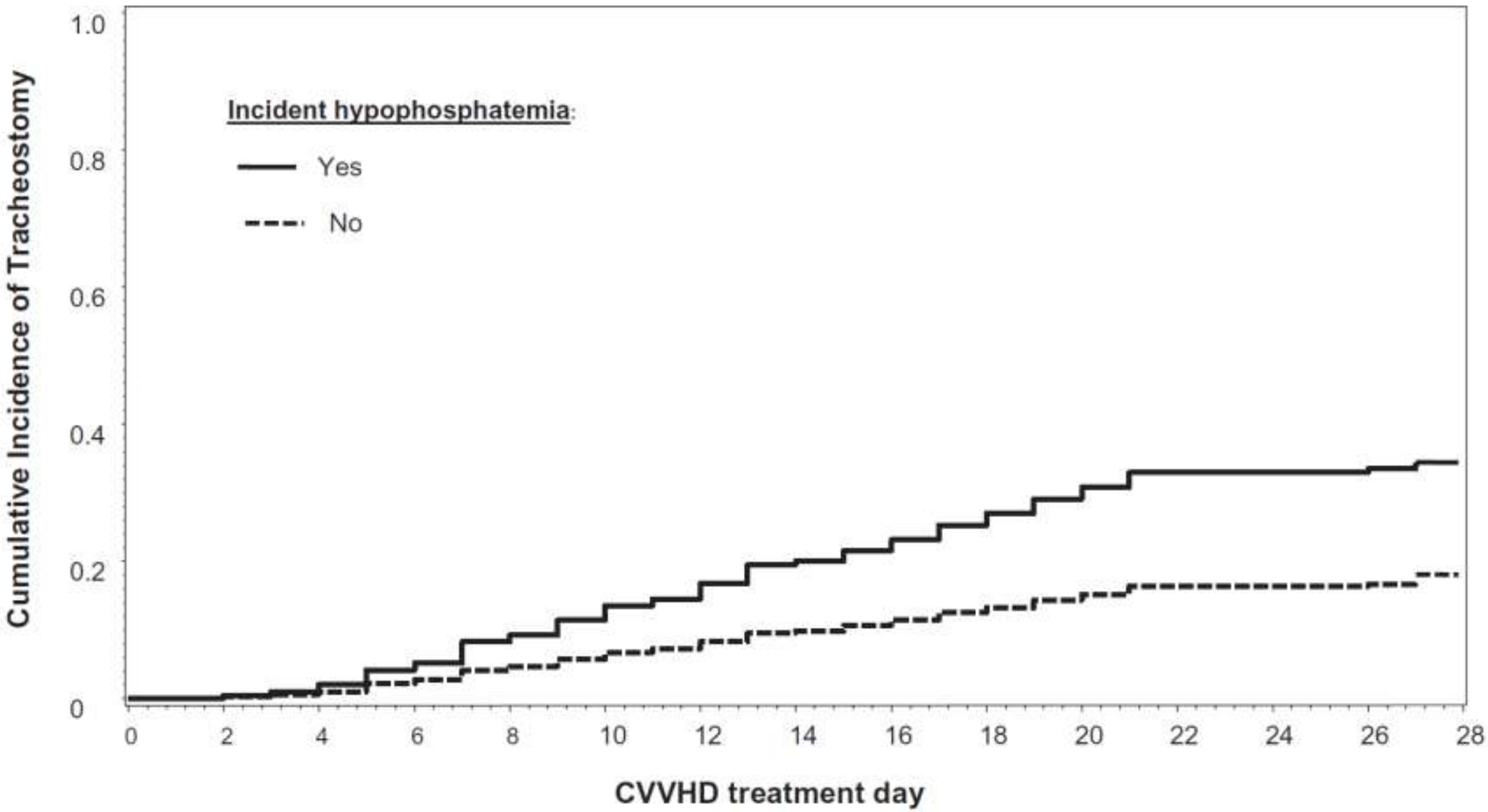

Demirjian et al NDT 2011

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

	Higher Intensity (n=722)	Lower Intensity (n=743)	p
Hypo – PO4 (%)	65.1	54.0	<0.001
Hypo – K (%)	23.4	24.4	0.34

Bellomo et al NEJM 2009

Phosphate-containing dialysis solution prevents hypophosphatemia during continuous renal replacement therapy

M. Broman[1], O. Carlsson[2], H. Friberg[1], A. Wieslander[2] and G. Godaly[2]
[1]Department of Anaesthesiology and Intensive Care, Lund University Hospital, Lund, Sweden and [2]Gambro Lundia AB, Lund, Sweden

	Hemosol B0 (mmol/l)	Phosphate containing dialysis solution (mmol/l)
Bicarbonate	32	30
Lactate	3	0
Calcium	1.75	1.25
Magnesium	0.5	0.6
Potassium	0	4
Sodium	140	140
Phosphate	0	1.2
Chloride	109.5	115.9

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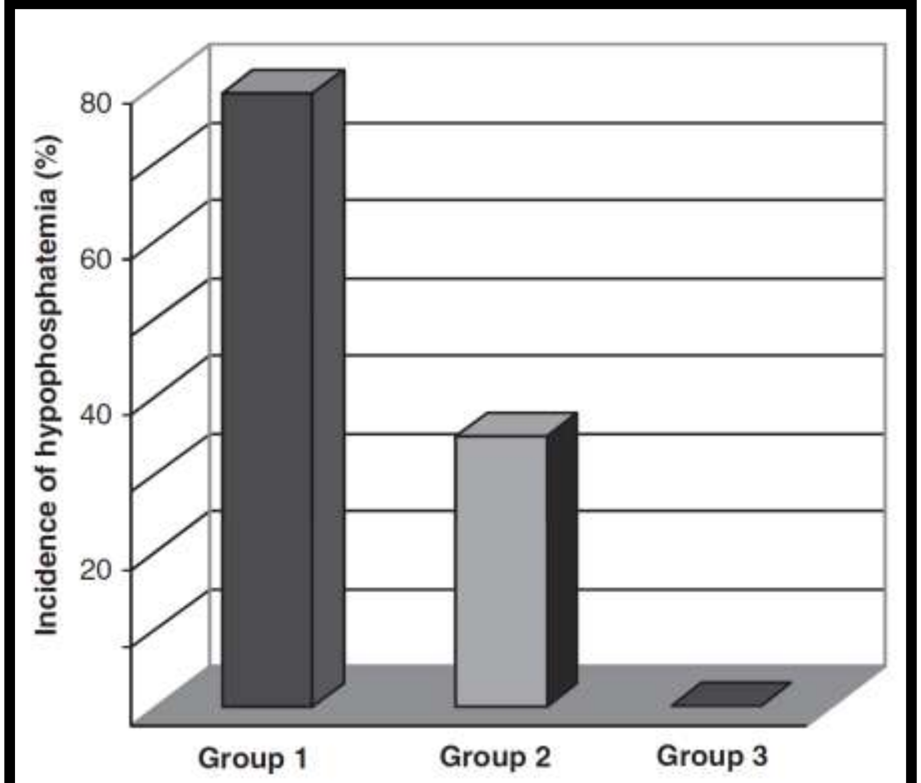
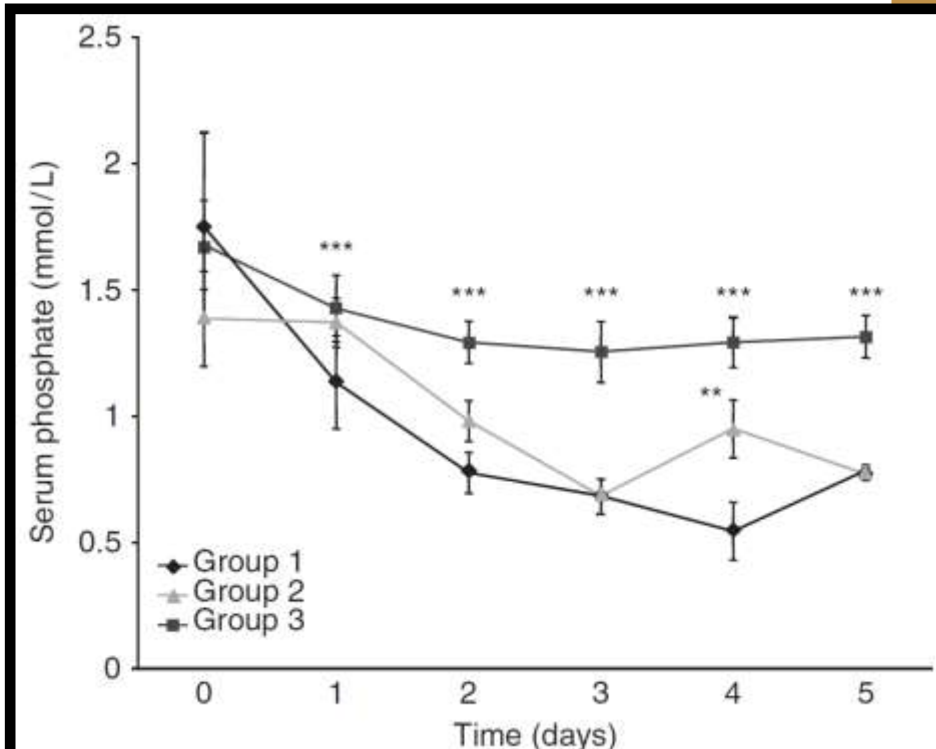


Hemosol BO only	Hemosol BO + Phoxilium	Phoxilium only



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	Hemosol BO (n=14)	Hemosol BO + Phoxilium (n=14)	Phoxilium (n=14)
Supplemental PO4 (mmol/day CRRT)	11 (0-35)	3 (0-13)	0 (0)

Substitution Fluid Safety

- Custom fluid preparation:
  - Local pharmacy or bedside
  - Prone to preparation error
  - Issues with sterility/endotoxin

MEDICAL ERROR

Responding to tragic error: lessons from Foothills Medical Centre

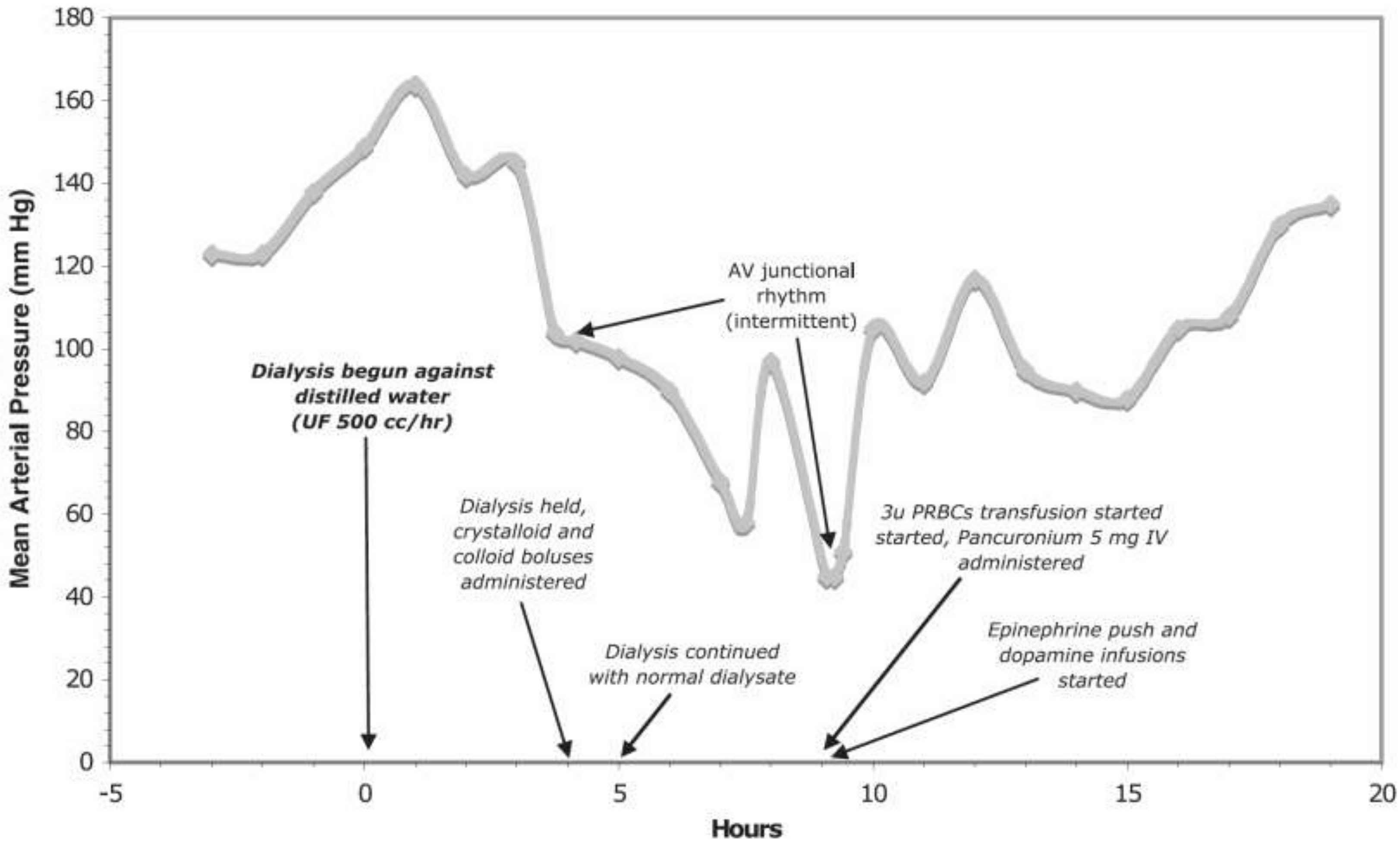
Sodium Chloride

Potassium Chloride

Johnson et al CMAJ2004

Hemolysis due to inadvertent hemodialysis against distilled water: Perils of bedside dialysate preparation

Jacob M. Pendergrast, MD, FRCPC; Michelle A. Hladunewich, MD, FRCPC;
Robert M.A. Richardson, MD, FRCPC



Pendergrast et al CCM 2006

Substitution Fluid Standards

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Fluid Type	Bacteria (cfu/mL)	Endotoxin (EU/mL)
Dialysate	<200	<2
Ultrapure	<0.1	<0.03
On-line Substitution	<1 x 10^6	<0.03
Sterile (commercial)	Validated Sterilization Procedure/Testing	

Serum [Na+] Disorders in CRRT

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- **Methods to prevent rapid serum [Na+] shift:**
  - Reduce CRRT efficiency by decreasing BFR and/or total effluent (UF) rate
  - Alter [Na+] of replacement/dialysate fluid
    - Custom solution (Pharmacy)
    - Alter a commercially prepared solution (Bedside)
- **CRITICAL – [Na+] must be monitored**
  - Not able to reliably predict how [Na+] will correct

Addition of [NaHCO3] to Fluid

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[Na+] (mEq/L)	Volume (mL)	HCO3 added (mmol/L)	[HCO3] (mmol/L)
110	4750	-	
140	5000	160	32
149	5050	50	42
157	5100	50	52

The HYPOnatremic Patient

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- Need to reduce replacement/dialysate [Na+]
  - Prevent/mitigate risk of ODS

- Two methods:
  1. *Alter replacement/ dialysate fluid* by the addition of fixed volume of D5W (sterile H20)
  2. *Administer a separate infusion of D5W* on PBP to dilute replacement fluid (effectively removed via UF)

Replacement ↓ [Na+] Adjustment

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Fluid [Na+] (mEq/L)	UF Rate (mL/hr)	D5W PBP Rate (mL/hr)	Effective Fluid [Na+] (mEq/L)
140	2000	100	133
140	2000	150	130
140	2000	200	127
140	2000	250	124
140	3000	100	135
140	3000	150	133
140	3000	200	131
140	3000	250	129

The HYPERnatremic Patient

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- Need to increase replacement/dialysate [Na+]
  - Prevent/mitigate risk of cerebral edema
- Two methods:
  1. *Alter replacement/dialysate fluid* by the addition of fixed volume of hypertonic saline
  2. *Administer a separate infusion of saline solution* on PBP to increase replacement fluid [Na+]

Replacement ↑ [Na+] Adjustment

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Fluid [Na+] (mEq/L)	3% HS (mL)	Na+ added (mmol)	End [Na+] (mmol/L)
140	0	0	140
140	50	25.7	144
140	100	51.3	147
140	150	77.1	151
140	200	102.8	155
140	250	128.5	158

CRRT Fluid Options (Gambro)

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Electrolytes (mmol/l)	*Bicarbonate*							*Lactate*			*Citrate*		
	Hemosol B0 Prismasol 0	Prismasol 2	Prismasol 4	Phoxilium	Dialisan	Prism0cal	Prism0cal B22	Lactasol	Hemosol LG2 (Kalilactasol)	Hemosol LG4 (Hemolactol)	Prismocitrate 10/2	PrismoCit 4K	Prismocitrate 18/0
HCO3	*32*	*32*	*32*	*30*	*32*	*32*	*22*	*0*	*0*	*0*	*0*	*0*	*0*
Lactate	*3*	*3*	*3*	*0*	*3*	*3*	*3*	*40*	*40*	*40*	*0*	*0*	*0*
Citrate	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*10*	*10*	*18*
Citric Acid	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2*	*2*	*0*
Na+	*140*	*140*	*140*	*140*	*140*	*140*	*140*	*140*	*142*	*140*	*136*	*140*	*140*
K+	*0*	*2*	*4*	*4*	*2*	*0*	*4*	*0*	*2*	*4*	*0*	*4*	*0*
Ca++	*1.75*	*1.75*	*1.75*	*1.25*	*1.75*	*0*	*0*	*1.75*	*1.75*	*1.75*	*0*	*0*	*0*
Mg++	*0.5*	*0.5*	*0.5*	*0.6*	*0.5*	*0.5*	*0.75*	*0.75*	*0.75*	*0.75*	*0*	*0*	*0*
Cl-	*109.5*	*111.5*	*113.5*	*116*	*111.5*	*106*	*120.5*	*105*	*109*	*109*	*106*	*114*	*86*
Phosphate	*0*	*0*	*0*	*1.2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
Glucose	*0*	*6.1*	*6.1*	*0*	*6.1*	*0*	*6.1*	*0*	*6.1*	*6.1*	*0*	*0*	*0*
Class	Drug	Drug	Drug	Drug	*MD*	*MD*	*MD*	Drug	Drug	Drug	*MD*	*MD*	*MD*

Courtesy of Gambro

NOTICE TO HOSPITALS
Health Canada Endorsed Important Safety Information on Accusol 35 Haemodialysis Solutions for Acute Renal Therapy

Edwards

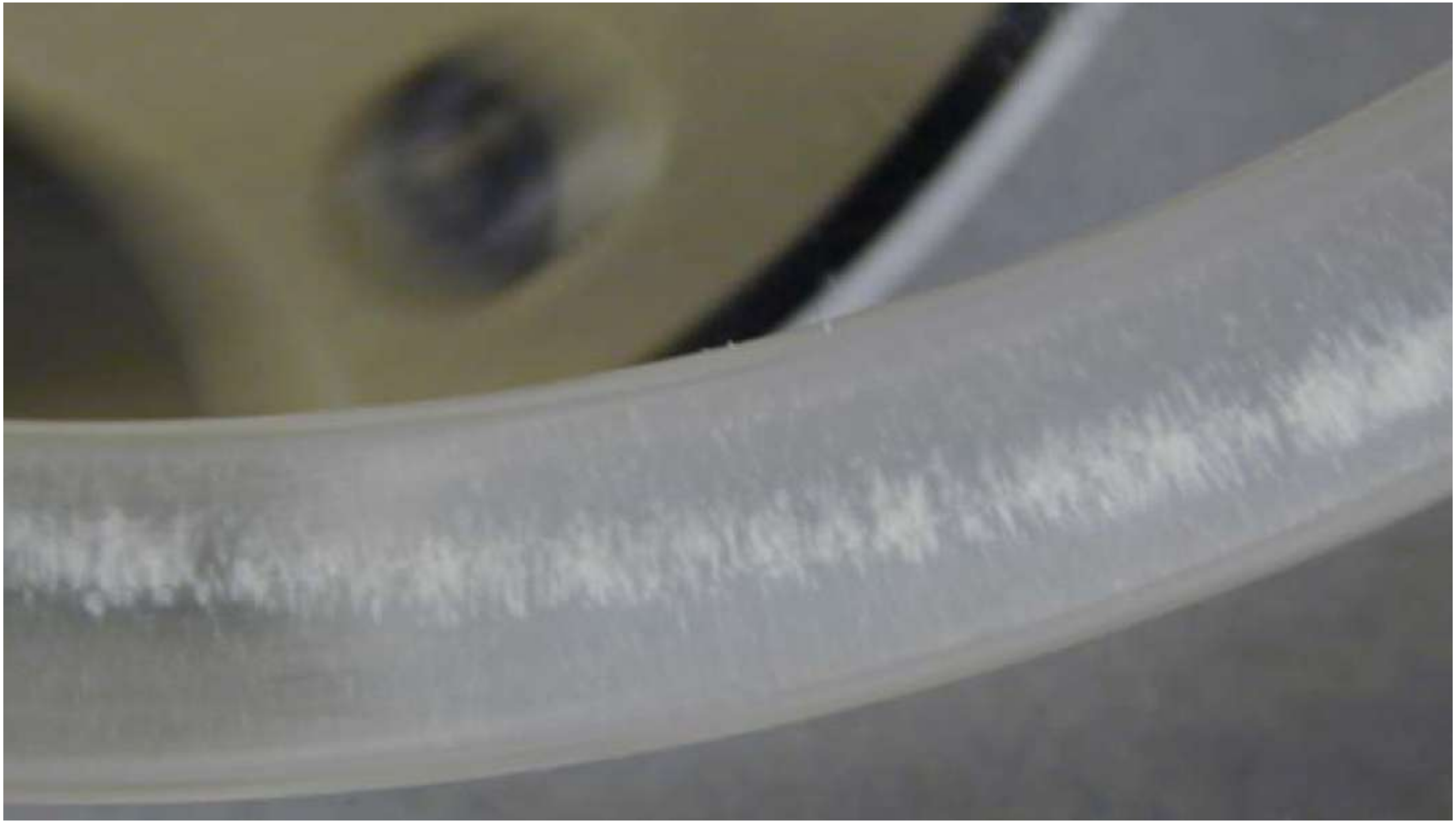
2008/08/01

Subject: **Risk of precipitate formation with Accusol™ 35 Haemodialysis solutions when used for Haemofiltration and Haemodiafiltration treatment modes.**

Edwards Lifesciences in consultation with Health Canada would like to advise you that precipitate formation has been observed in ACCUSOL 35 haemodialysis solutions for acute renal therapy when these solutions are used for treatment modes other than haemodialysis.

- **Accusol 35 solutions should only be used for the haemodialysis treatment mode, the approved indication in Canada, in accordance with the product labeling.**
- **Accusol 35 solutions should not be used for haemofiltration and haemodiafiltration treatment modes, due to potential risk from the observed precipitate. In Canada, these treatment modes are not approved for Accusol 35 hemodialysis solutions.**

CaCO3 Precipitation



Available at: www.hc-sc.gc.ca

CRRT Fluid Options (Dialysis Solutions)

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NORMOCARB HF	NC 25 HF	NC 35 HF
HCO3	25	35
Lactate	0	0
Na+	140	140
K+	0	0
Ca++	0	0
Mg++	1.5	1.5
Cl-	116.5	106.5
Phosphate	0	0
Gluc/Dext	0	0
Undiluted/diluted Vol	240 mL (3.24 L)	240 mL (3.24L)

Available at: www.normocarb.com

Clinical Outcome Following the Use of Inadequate Solutions for Continuous Veno-Venous Hemodiofiltration

Jale Bengi Celik, Ahmet Topal, Elmas Kartal, and Alper Yosunkaya

Faculty of Medicine & Dentistry
University of Alberta

Variable	1.36% PD	HCO3-buffer	P-value
Serum HCO3 (mmol/L)	20.9	23.5	<0.05
Serum Lac- (mmol/L)	7.6	2.9	<0.05
Base Excess	-6.2	-2.2	<0.05
Hypotension (%)	71	40	<0.05
Hyperglycemia (%)	64	30	<0.05
Metabolic acidosis (%)	57	30	<0.05
Insulin (U/kg/h)	0.2	0.07	<0.05
HCO3 extra (mmol/d)	13.8	6.2	<0.05

Celik et al Rena Fail 2008

Summary

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- Impossible to have a standardized fluid suitable for all critically ill patients
- Ideal CRRT substitution fluid:
  - Composition ≈ Plasma
  - Replacement ≈ Dialysate
- Commercial substitution fluids
  - Reduced risk of error
  - More expensive

Summary

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- Base Buffer → $HCO3$
- Mitigate GLUCOSE loss by glycemic control
- Protein 1.5-1.8 g/kg/d
  - Glutamine supplementation
- Vitamins
  - Supplementation
- Trace elements (water-soluble)
  - Supplementation (thiamine/selenium)
- Cascade hemofiltration?

Thank You For Your Attention!

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Questions?

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