When and How I Prescribe CRRT

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DISCLOSURES

- Ravindra L Mehta MD
- Speaker
- I had a personal financial relationship with commercial entities during the last two years :

- Baxter, AM Pharma, CSL- Behring, Astute Medical Inc. Regulus, Akebia, Intercept, Mallinckrodt, Ferring
- Grants: Relypsa, Fresenius-Kabi; Fresenius, Grifols

CRRT When and How

CRRT Attributes → *Matching Therapy to Clinical Need* → *Prescription and Delivery*

CRRT When and How

CRRT Attributes

Matching Therapy to Clinical Need

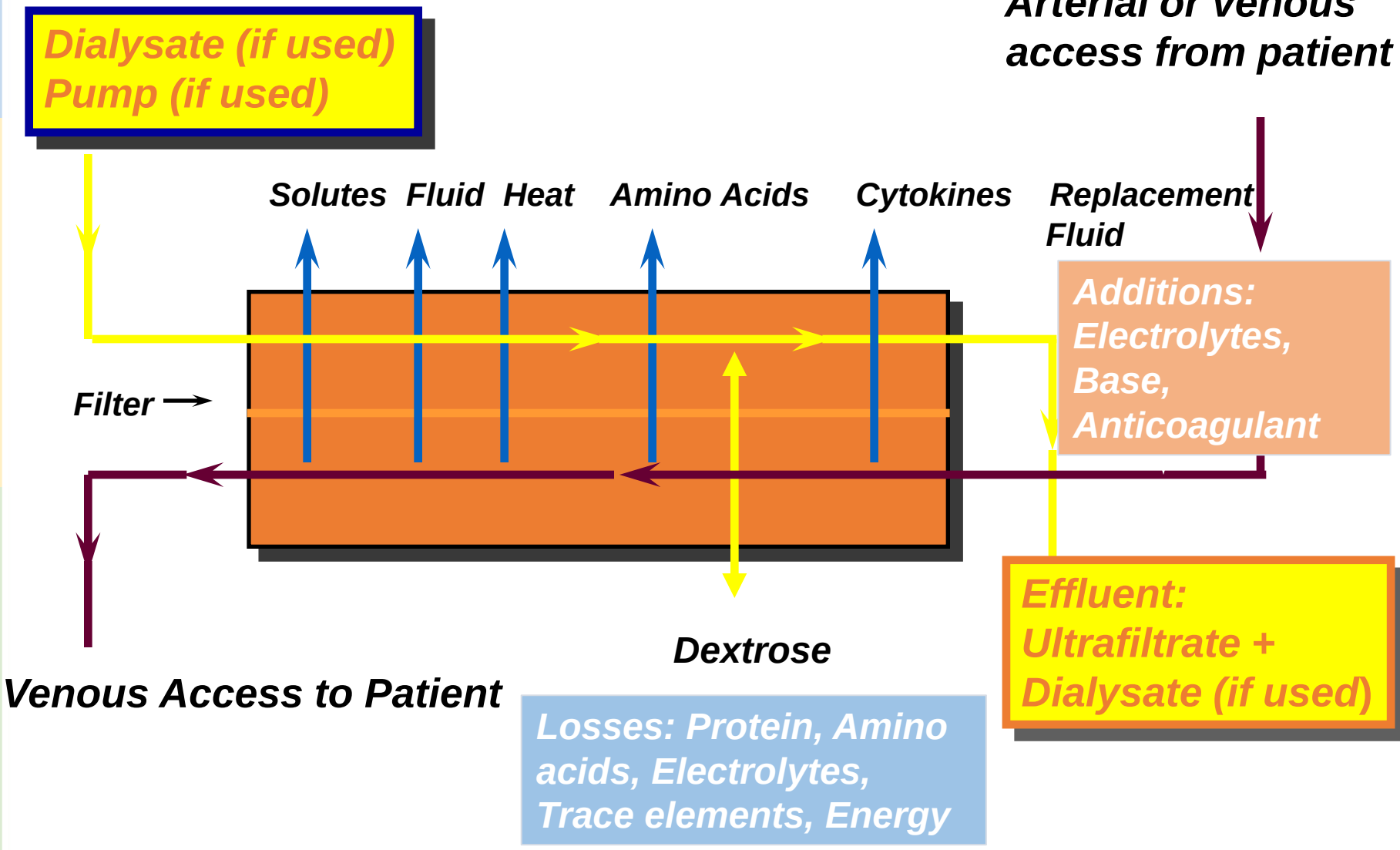
Prescription and Delivery

The case for CRRT?

How can CRRT be utilized

- To remove solutes and fluid
- To add solutes and fluid
- For regulation of volume and plasma composition
- To prevent toxicity

RRT Schematic
Blood/Bath Transfer



Key Considerations for RRT applications

Therapeutic Targets

- Solute Homeostasis
- Fluid Regulation
- Biologic effects
  - Hemodynamics
  - Cytokines
  - Cell function
  - Metabolic control

Operational Characteristics

- Solute clearance
  - Electrolytes
  - Acid Base Balance
  - Amino acid removal
  - Drug therapy
- Fluid regulation
  - Space
  - Pressor support
- Modulation of Mediators
  - Removal of toxic factors
  - Adsorption
- Thermal Control
  - Hemodynamic support
  - Cerebral Edema

Specific Features of CRRT

Available time 24 hrs/day

- Provide time for organ failure to resolve
- Treat underlying cause
- Enable dynamic adjustments and control

Flexibility

- Multiple modalities
- Variation in operational characteristics according to need
- Dissociated fluid and solute control

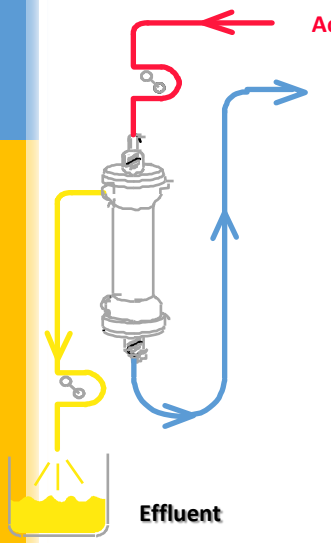
Organ Support

- Targeted interventions
- Disease modification

Multidisciplinary approach

- Interaction to define goals
- Drug management
- Nutritional support
- Trial of therapy

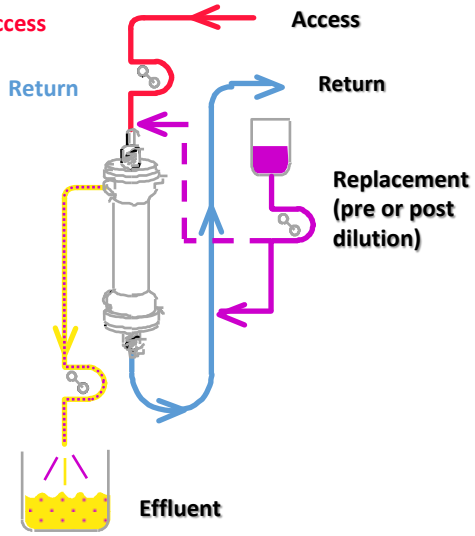
CRRT Modalities



SCUF

No solute clearance;

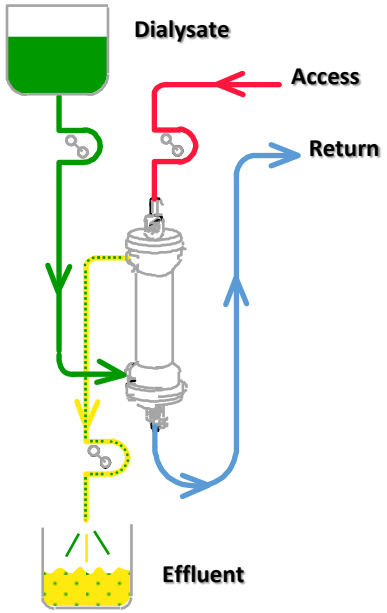
Used for fluid removal



CVVH

Solute clearance: convection;

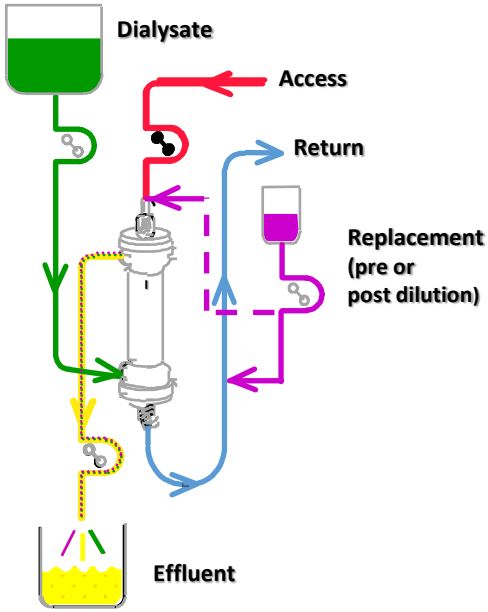
Operative fluid: RF



CVVHD

Solute clearance: diffusion;

Operative fluid: dialysate



CVVHDF

Solute clearance: diffusion & convection;

Operative fluids: RF & dialysate

CRRT Operational Characteristics

CVVHDF

CVVHD

CVVH

Clearance in CRRT = SC or equivalent x effluent volume (UF, dialysate, UF + dialysate) + membrane adsorption

Dialysate

Diffusive clearance

Ultrafiltrate

Convective Clearance

Effluent

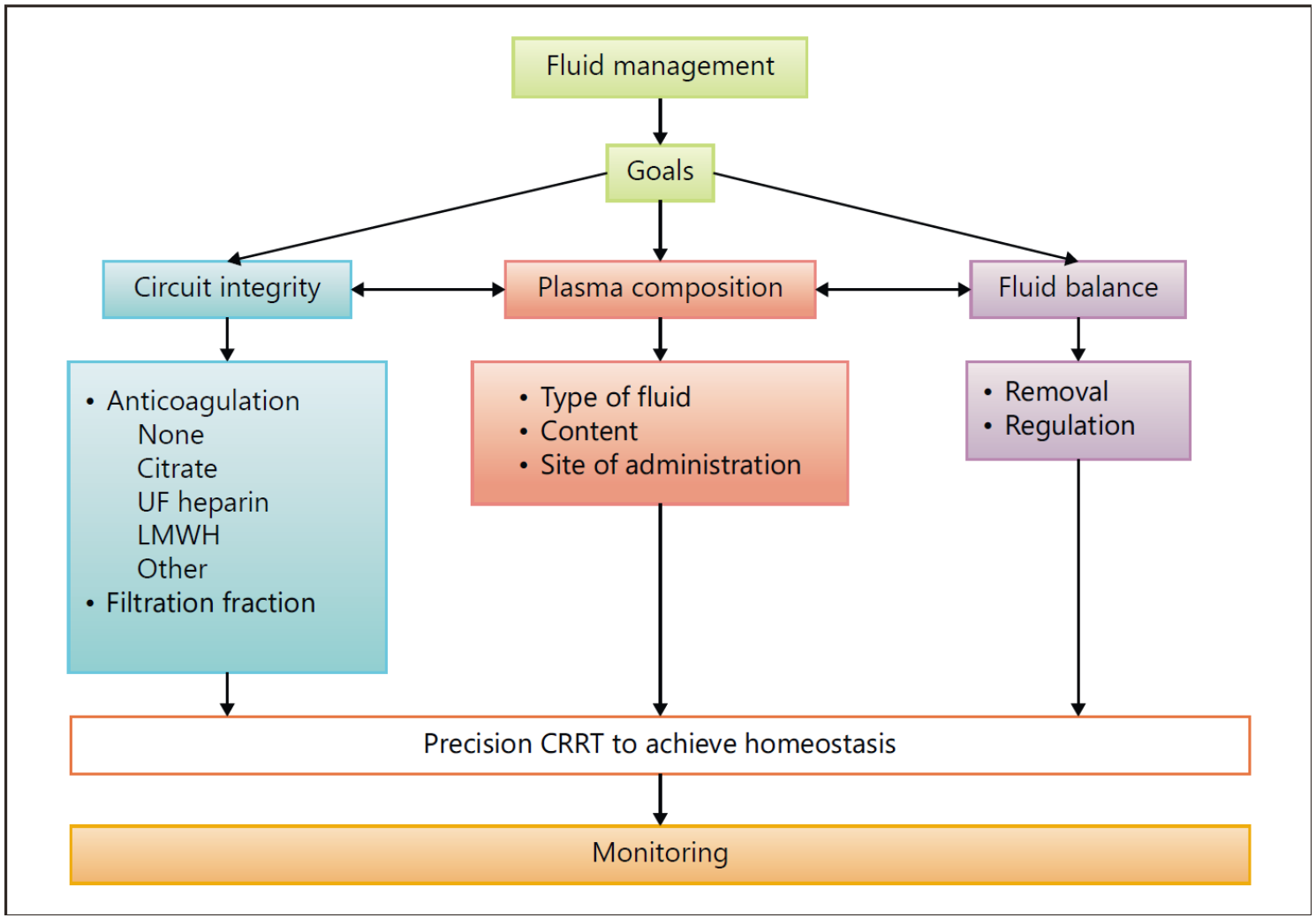
(Total fluid in waste bag at end of a time period.)

Sieving Coefficient = UF/Plasma concentration of solute

(1= freely permeable, 0+ not permeable).

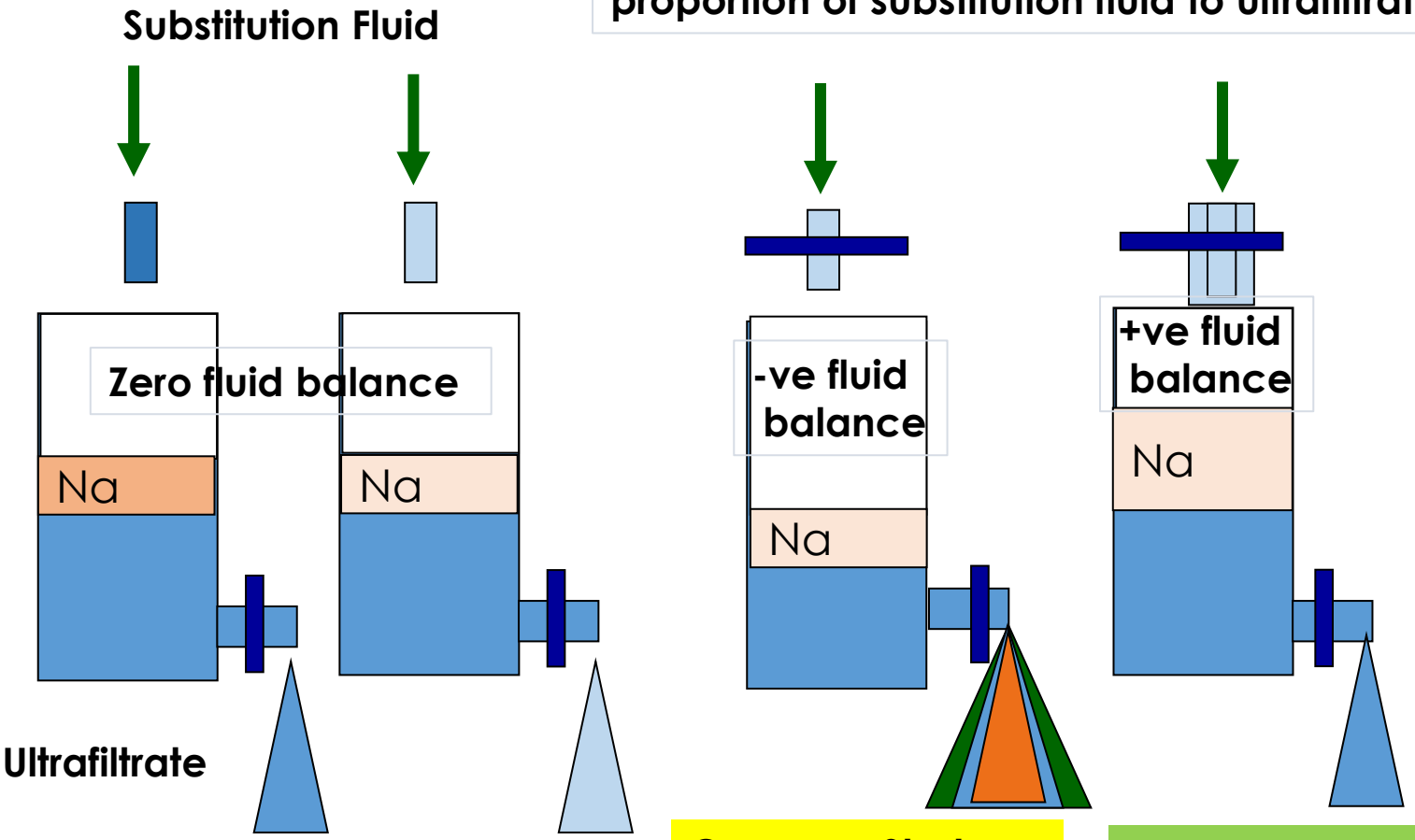
Dialyzer and blood clearance differ based on solute and membrane characteristics

Fluid Management with CRRT



Approaches to Solute and Fluid Homeostasis with CRRT

Fluid balance is achieved by altering the proportion of substitution fluid to ultrafiltrate



Solute homeostasis is achieved by altering composition of substitution fluid or dialysate

Common Strategy
UF is Varied

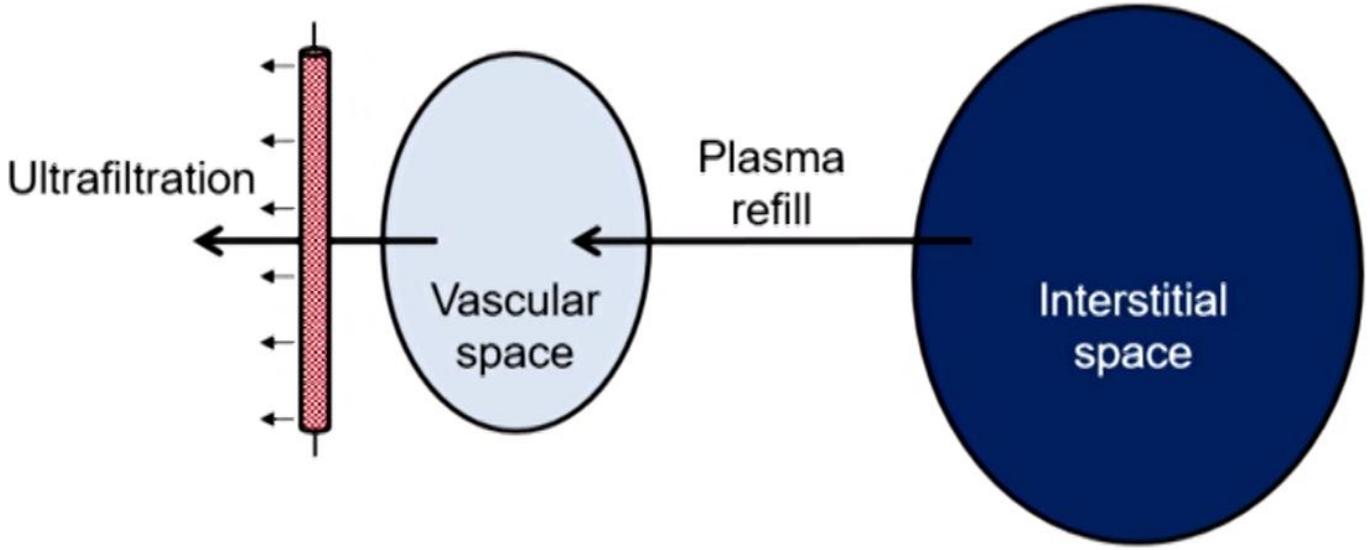
Alternate Strategy

UF is fixed
Replacement is varied

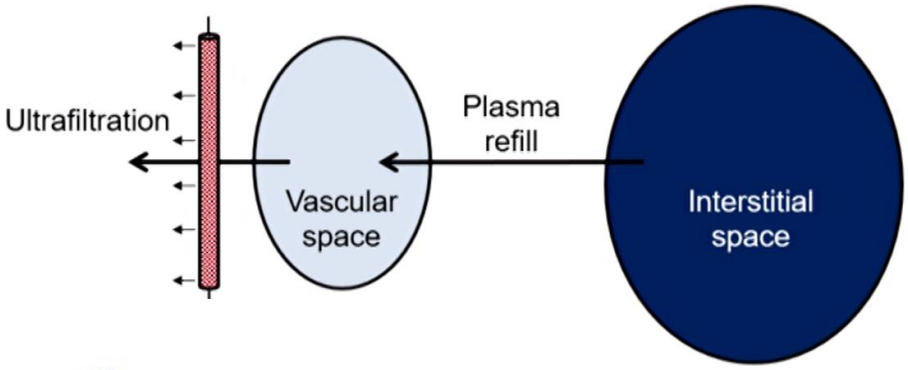
Key feature of CRRT is the ability to control solute and fluid balance independently

What can we do in CRRT?

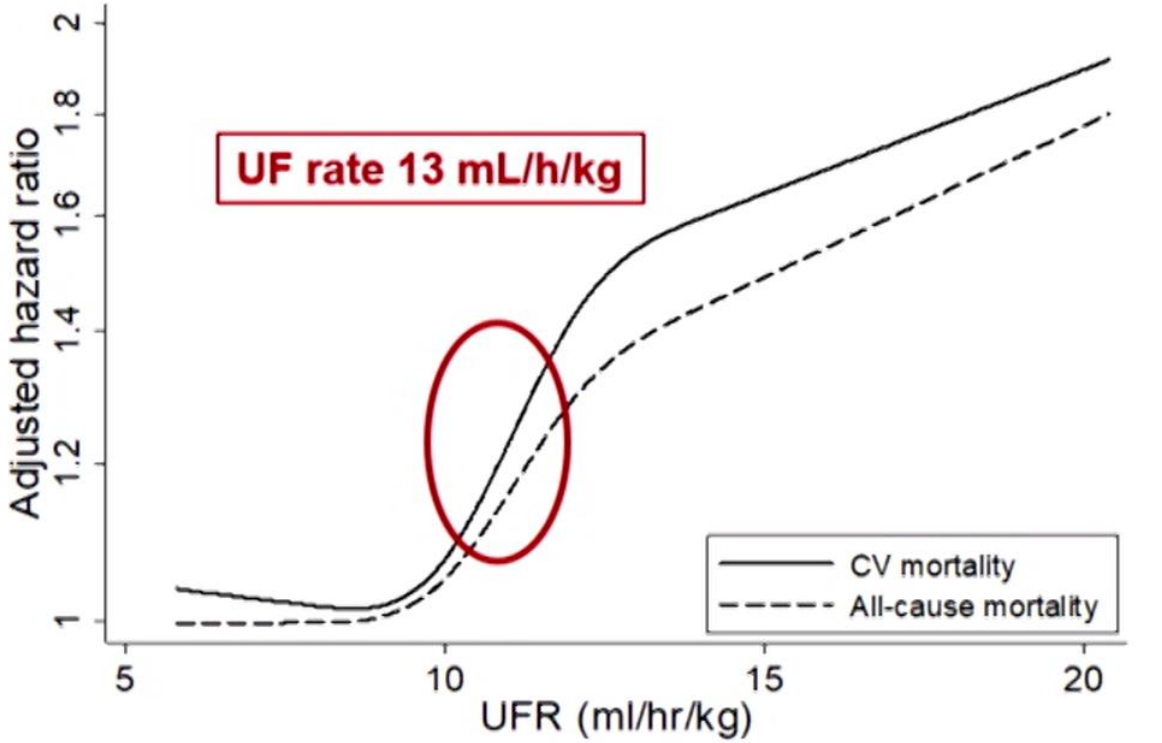
UF rate > plasma refill rate → hypotension



Higher UF Rate Associated with Death



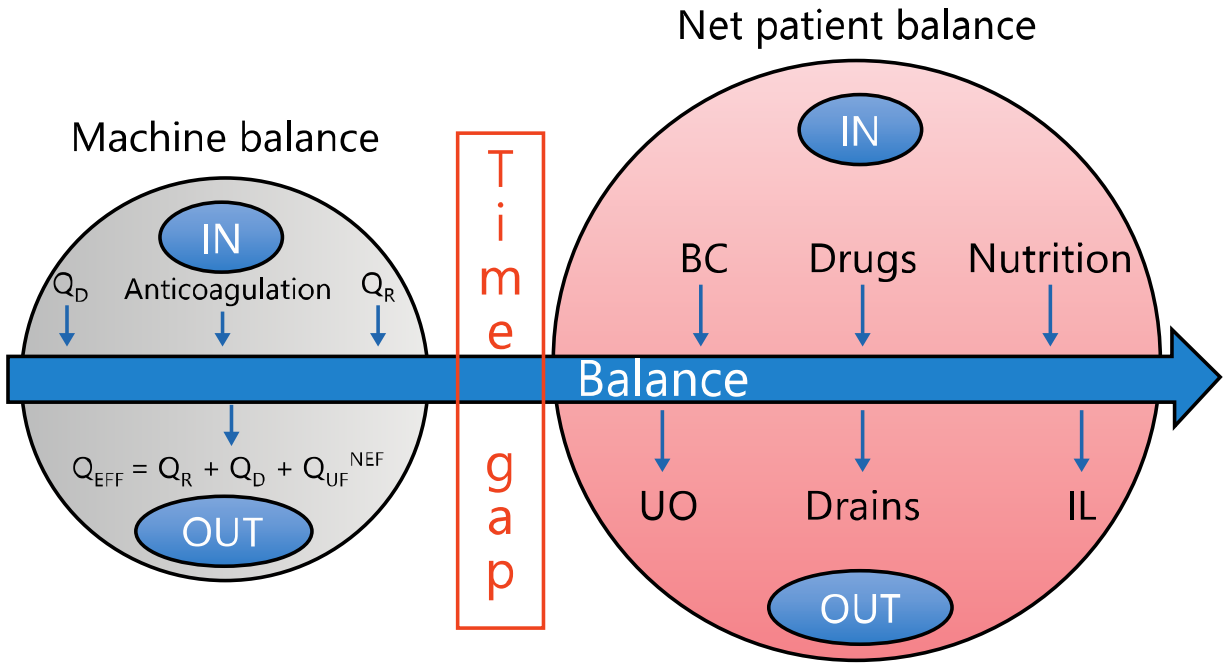
Higher UF rate → death



Flythe et. Al Kid Int, 2011

Approaches to Fluid Balance with CRRT
Fluid Regulation

Ultrafiltrate volume limited to match anticipated needs for fluid balance over 8-24 hours.



Blood Purif 2016;42:266–278

Fluid Assessment and CRRT Prescription

Hourly Assessment

- ✓ Ultrafiltrate volume adjusted every hour to achieve targeted patient fluid balance.
- ✓ Ultrafiltrate volume adjusted every hour to achieve targeted specific hemodynamic parameters e.g. CVP, PAWA, MAP.

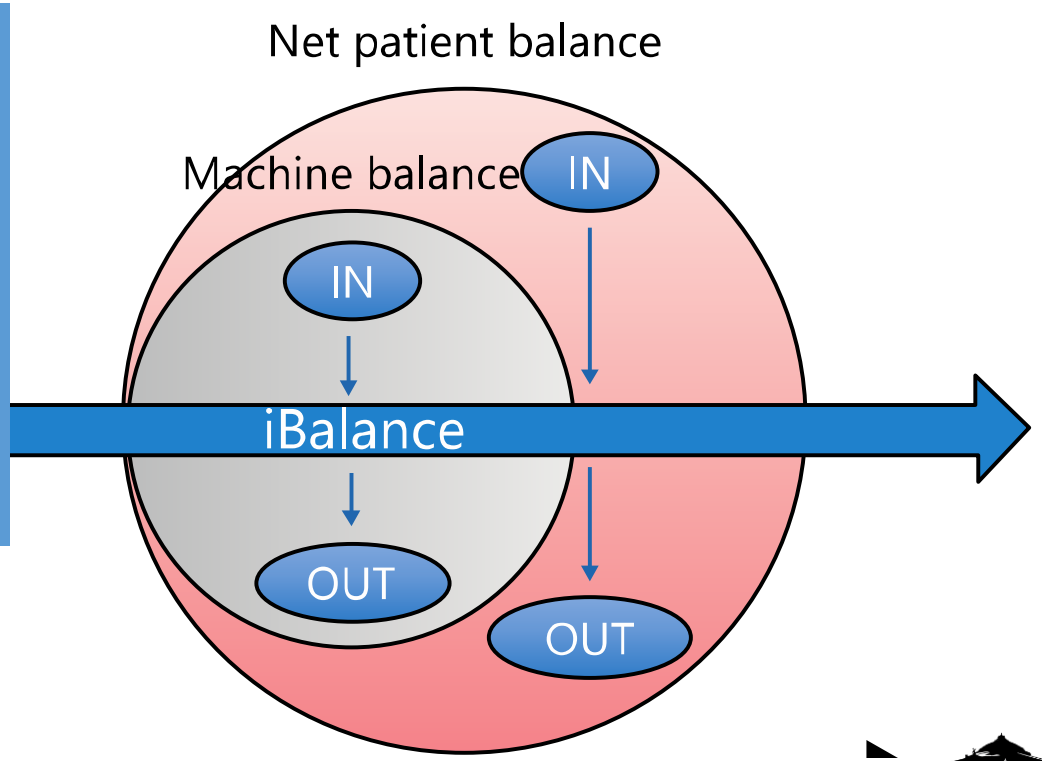
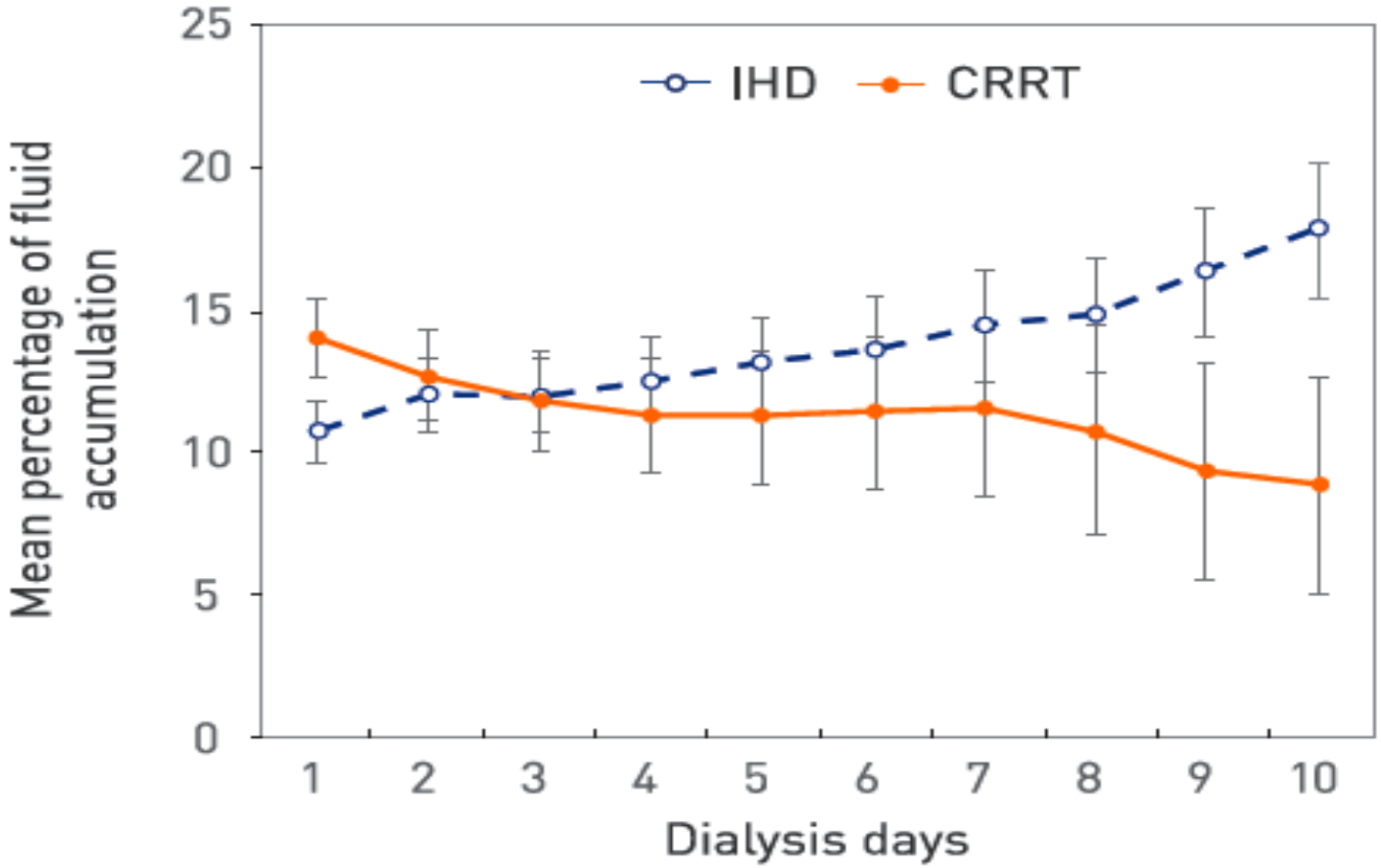


Figure 4: Effect of Dialysis Modality on Fluid Balance



Bouchard et al KI 2009;76:422-27

CRRT When and How

CRRT Attributes

Matching Therapy to Clinical Need

Prescription and Delivery

When is CRRT usually considered?

Common scenarios for CRRT

- Oliguric fluid overloaded patient
- Hemodynamic instability
- High intake and difficulty in fluid removal
- Severe acid base disorders

Clinical Indications for CRRT

Organ Support

- Renal
- Cardiac
- Hepatic
- Respiratory
- Neurological
- Nutrition
- Thermal regulation

Disease modification

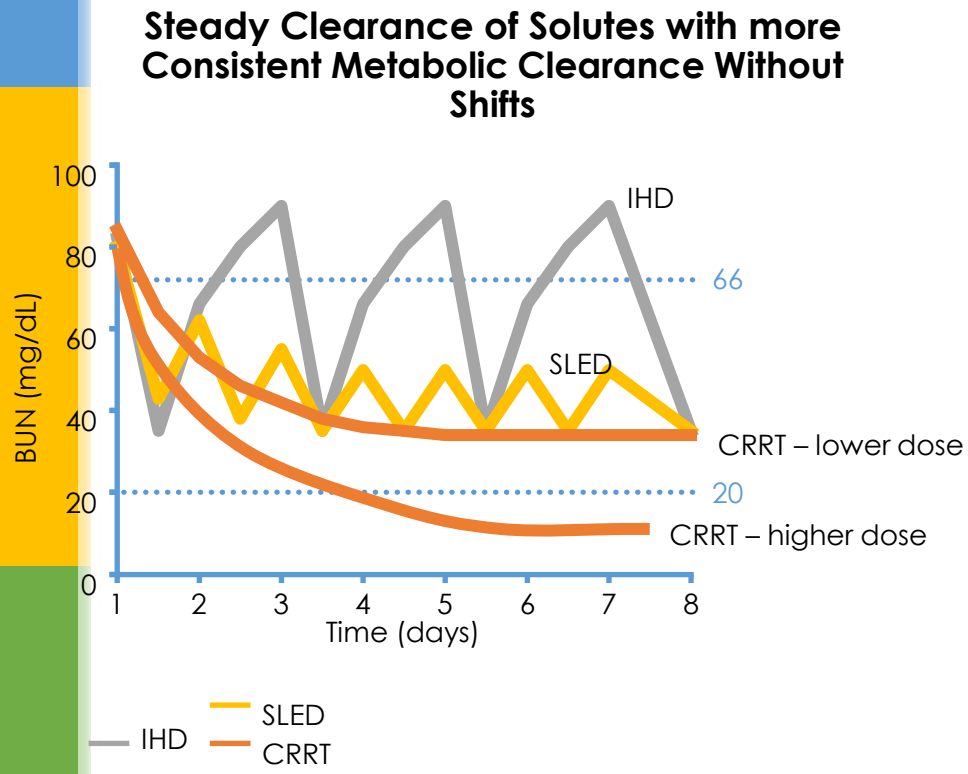
- Sepsis
- Metastatic Cancer
- Metabolic disorders

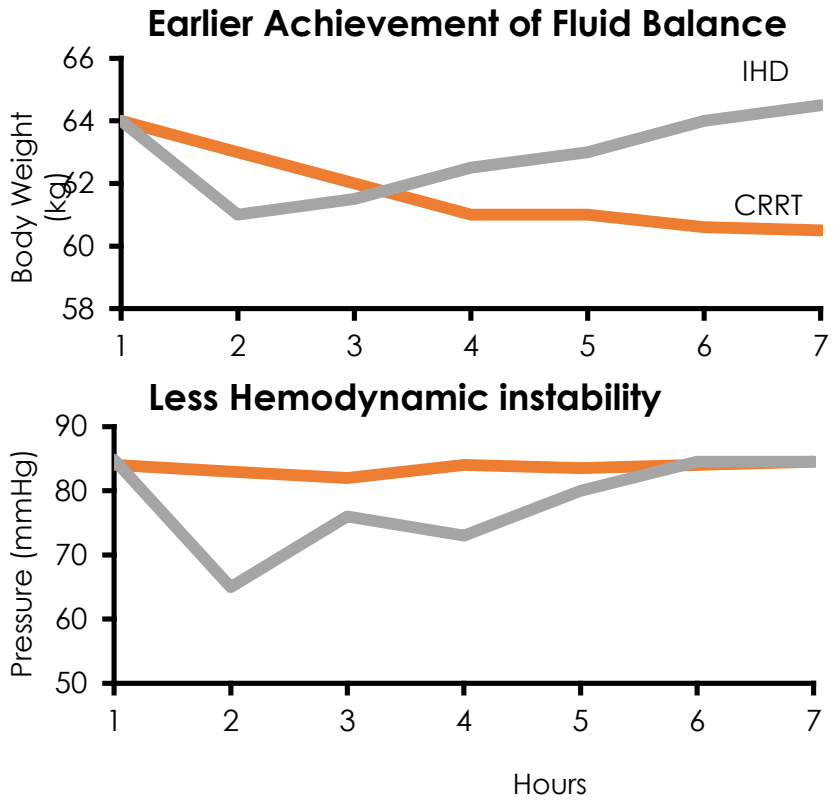
CRRT for Renal Support

Impaired Renal Function

- Rationale is to add capacity for solute clearance, fluid removal and achieve electrolyte and acid base homeostasis
- Remove toxins including drugs and metabolites e.g. phenobarbitol, methanol, lithium
- Allow time for renal functional recovery

Advantages of CRRT





Ronco C and Ricci Z. Intensive Care Med. 2008;34:2139–2146

Acid Base Balance in CVVH vs EDD

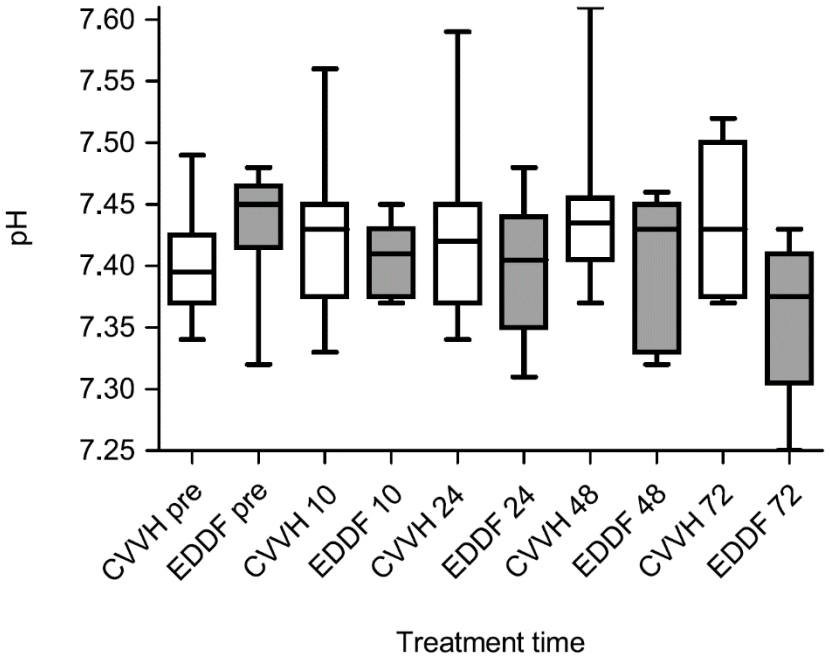


Fig. 3 Boxplot diagram of pH in arterial blood: before treatment (*pre*), at 10 h after treatment on day 1, and on days 2, 3 and 4 using EDDf ($n = 8$) or CVVH ($n = 8$). No significant differences

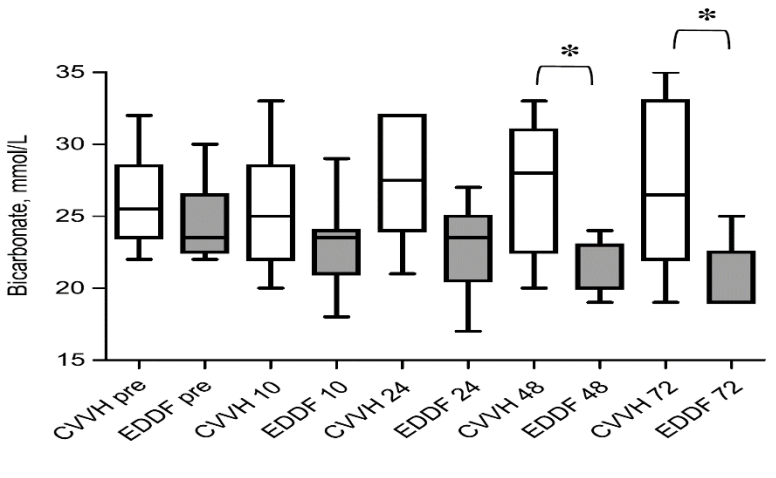


Fig. 4 Boxplot diagram of bicarbonate in arterial blood: before treatment (*pre*), at 10 h on day 1, and on day 2, day 3 ($p = 0.019$), and day 4 ($p = 0.039$) using EDDf ($n = 8$) or CVVH ($n = 8$)

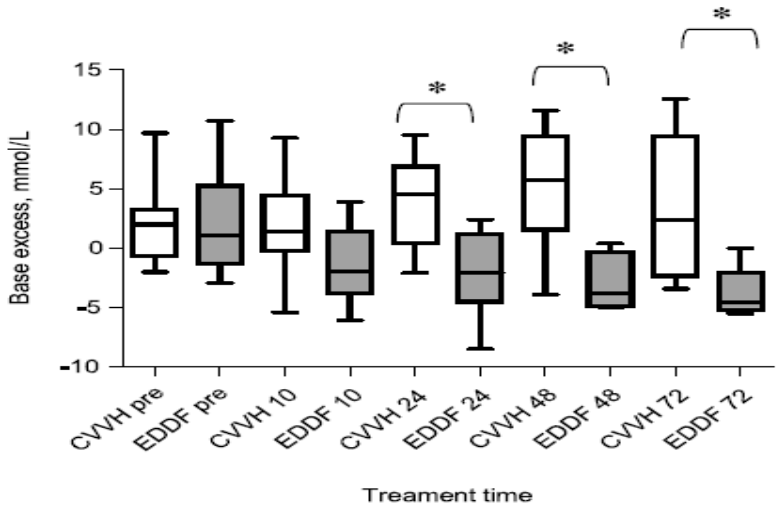


Fig. 5 Boxplot diagram of base deficit in arterial blood: before treatment (*pre*), at 10 h on day 1, and on day 2 ($p = 0.009$), day 3 ($p = 0.008$), and day 4 ($p = 0.033$) using EDDf ($n = 8$) or CVVH ($n = 8$)

Baldwin et al: Intensive Care Medicine 2007,

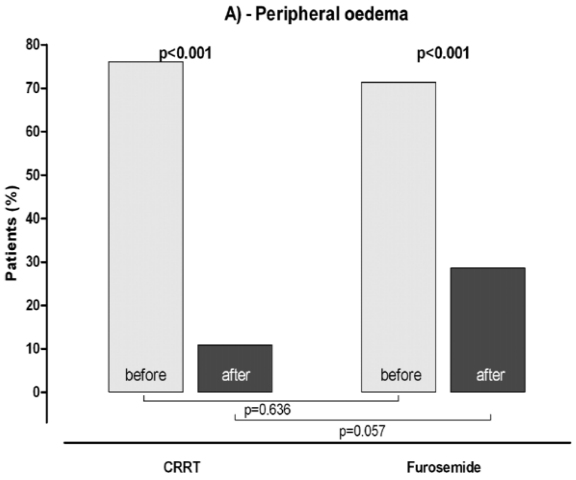
CRRT for Cardiac Support

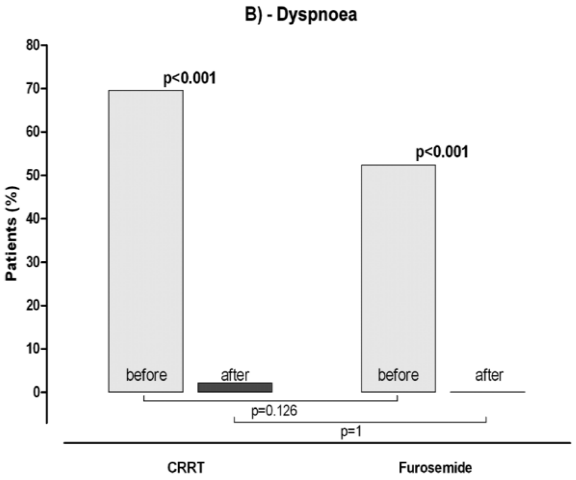
Cardiac Failure

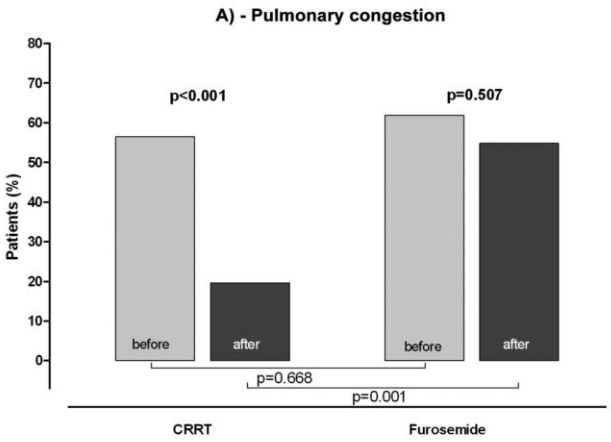
- Rationale is to remove fluid to restore cardiac function to Starling curve
- Facilitate hemodynamic support with vasopressors and inotropes
- ? Remove myocardial depressant factors

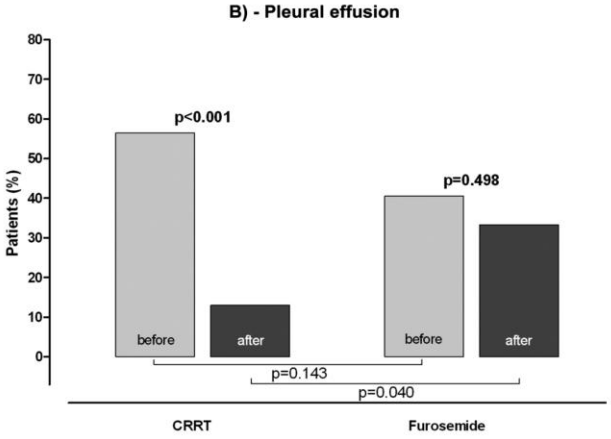
Congestive heart failure and decongestion ability of two different treatments: continuous renal replacement and diuretic therapy: experience of a cardiac step down unit

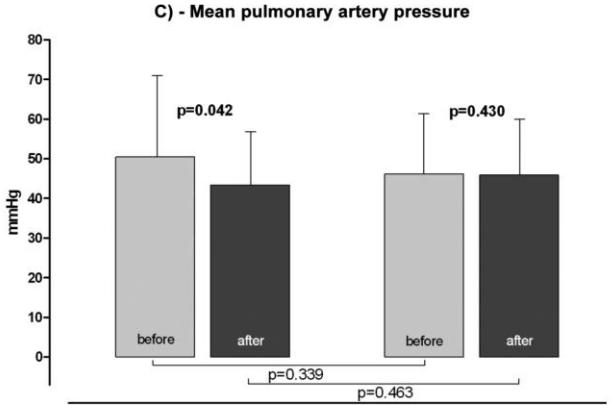
- In 88 patients with HF (NYHA class III-IV) we evaluated the effect of CRRT (n = 46) and intravenous diuretics (n = 42) on clinical and instrumental
- signs of congestion. A clinical score was obtained as the sum of signs and symptoms of HF to estimate the severity of each patient's clinical condition.
- The choice of diuretics or CRRT was guided by renal impairment or diuretics' resistance.











Acta Cardiologica, 68:4, 355-364, DOI: 10.1080/AC.68.4.2988888

CRRT for Liver Failure

Key Features of Liver failure

- Hyponatremia, ascites and hypotension
  - Compartment syndrome and hypotension worsen brain edema
- Fulminant liver failure and Hepatic Encephalopathy
  - Brain edema
  - Role of hyponatremia in worsening brain edema
  - Low urea concentration worsens chances of Osmotic Demyelination Syndrome
- Coagulopathy
  - Decreased or increased coagulation?

Stravitz RT CCM 2007;35:2498
Davenport A Contr Nephrol 2007;156:259
Davenport A Hemodial Int 2008;12:307

Słowiński et al. Critical Care (2015) 19:349
DOI 10.1186/s13054-015-1066-7

CRITICAL CARE

RESEARCH Open Access

Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (LiCAT) observational study

Table 3 RCA-CVVHD flows and citrate dose at start of treatment and end of observation

	Normal liver function (bilirubin ≤2 mg/dl)		Mild liver failure (bilirubin 2–7 mg/dl)		Severe liver failure (bilirubin ≥7 mg/dl)	
	Start	End	Start	End	Start	End
Blood flow (ml/min)	109 ± 24	114 ± 25	109 ± 25	117 ± 28	110 ± 24	107 ± 20
Dialysate flow (ml/h)	2144 ± 502	2292 ± 500	2128 ± 405	2328 ± 567	2008 ± 403	2310 ± 501
Net ul						
Citrate						

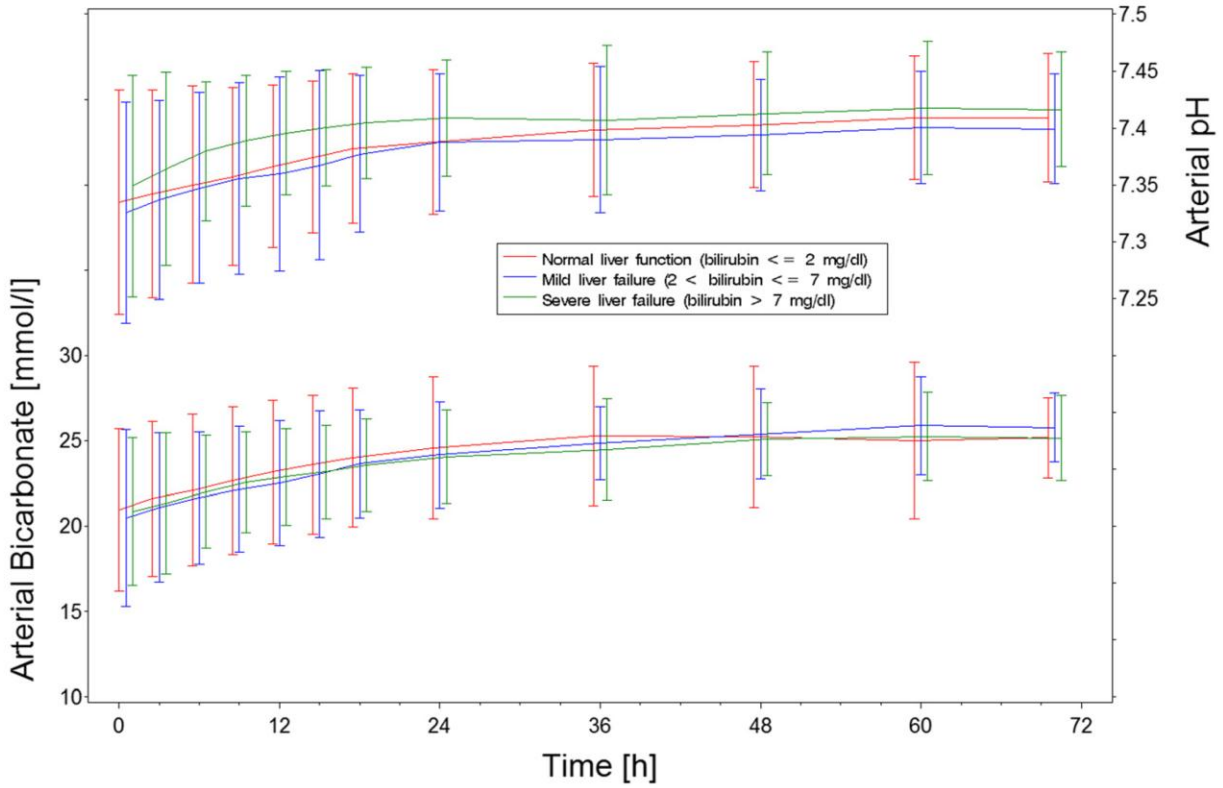


Fig. 2 Estimated mean ± standard deviation of arterial pH and serum bicarbonate concentrations during regional citrate anticoagulation and continuous venovenous hemodialysis according to liver groups

Fig. 1 Su
line: all fi

CRRT for Respiratory Support

ARDS

- Rationale is to optimize fluid status by regulating fluid balance and lung permeability.
- Patients with ARDS and Permissive Hypercapnia
  - Ventilatory support often requires permissive hypercapnia that results in acidemia. Concurrent use of CRRT can allow correction of acidemia without fluid or salt overload.
  - Citrate anticoagulation combined with addition of bicarbonate to dialysate allows compensation for respiratory acidosis

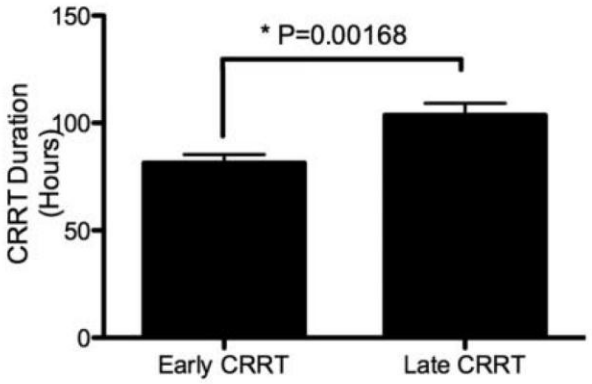
Han et al Early Initiation of CRRT Improves Clinical Outcomes in Patients With Acute Respiratory Distress Syndrome Am J Med Sci 2015;349(3):199–205.]

TABLE 1. Subjects' characte

	Early CRRT
Patients	27
Age	50.36 ± 16.97
Gender (M/F)	19/8
Causes of ARDS	

TABLE 2. Comparison of ve

	Early
PaO_2/FIO_2	121.45
PEEP ($cm \cdot H_2O$)	13.45
Plateau pressure ($cm \cdot H_2O$)	31.85



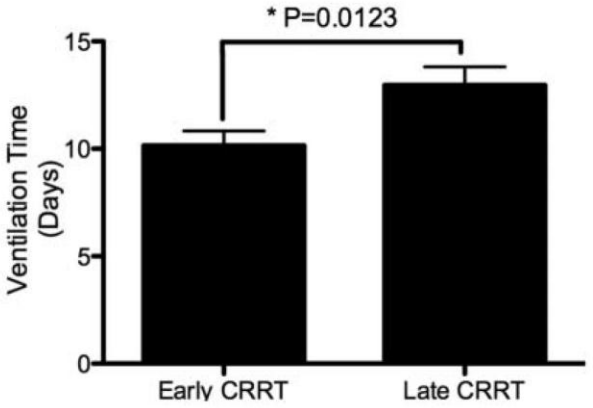


FIGURE 1. Comparison of duration of CRRT and mechanical ventilation between early initiation of CRRT and late initiation of CRRT groups. CRRT, continuous renal replacement therapy.

A-a gradient (mm Hg)	46.18 ± 11.12	44.09 ± 10.92	30.06 ± 13.13[c]	39.33 ± 15.71[a]	16.73 ± 11.92[c]	25.66 ± 12.39[ac]
Cdyn	17.18 ± 11.12	19.09 ± 12.31	20.06 ± 13.13	18.76 ± 10.08	32.73 ± 11.92	25.37 ± 10.27[a]
CVP (mm Hg)	14.09 ± 3.78	14.78 ± 4.09	11.90 ± 3.21[b]	15.01 ± 3.99[a]	9.91 ± 2.86[b]	10.57 ± 3.73[b]
MAP (mm Hg)	69.23 ± 25.1	71.15 ± 23.92	75.71 ± 23.9	70.63 ± 25.33	80.32 ± 27.5	77.93 ± 24.99
CI ($L \cdot min^{-1} \cdot m^{-3}$)	3.13 ± 1.27	2.95 ± 1.03	3.28 ± 1.16	2.76 ± 1.12	3.53 ± 1.20	3.12 ± 1.17
EVLWI (mL/kg)	15.26 ± 5.69	16.07 ± 5.35	10.26 ± 4.75[b]	13.99 ± 3.87[a]	5.05 ± 2.33[b]	6.77 ± 2.39[ab]
Fluid balance (mL)	163.31 ± 32.67	1058.27 ± 169.85[a]	50.38 ± 23.20[b]	595.18 ± 137.96[ab]	177.56 ± 40.31	183.67 ± 69.53[b]

[a] $P < 0.05$ compared with early CRRT at the same time point.
[b] $P < 0.05$ compared with baseline of day 0.
BALF, bronchoalveolar lavage fluid; Cdyn, dynamic compliance; CI, cardiac index; CVP, central venous pressure; EVLWI, extrtravascular lung water index; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure.

CRRT for Neurological Support

Intracranial Pressure Management

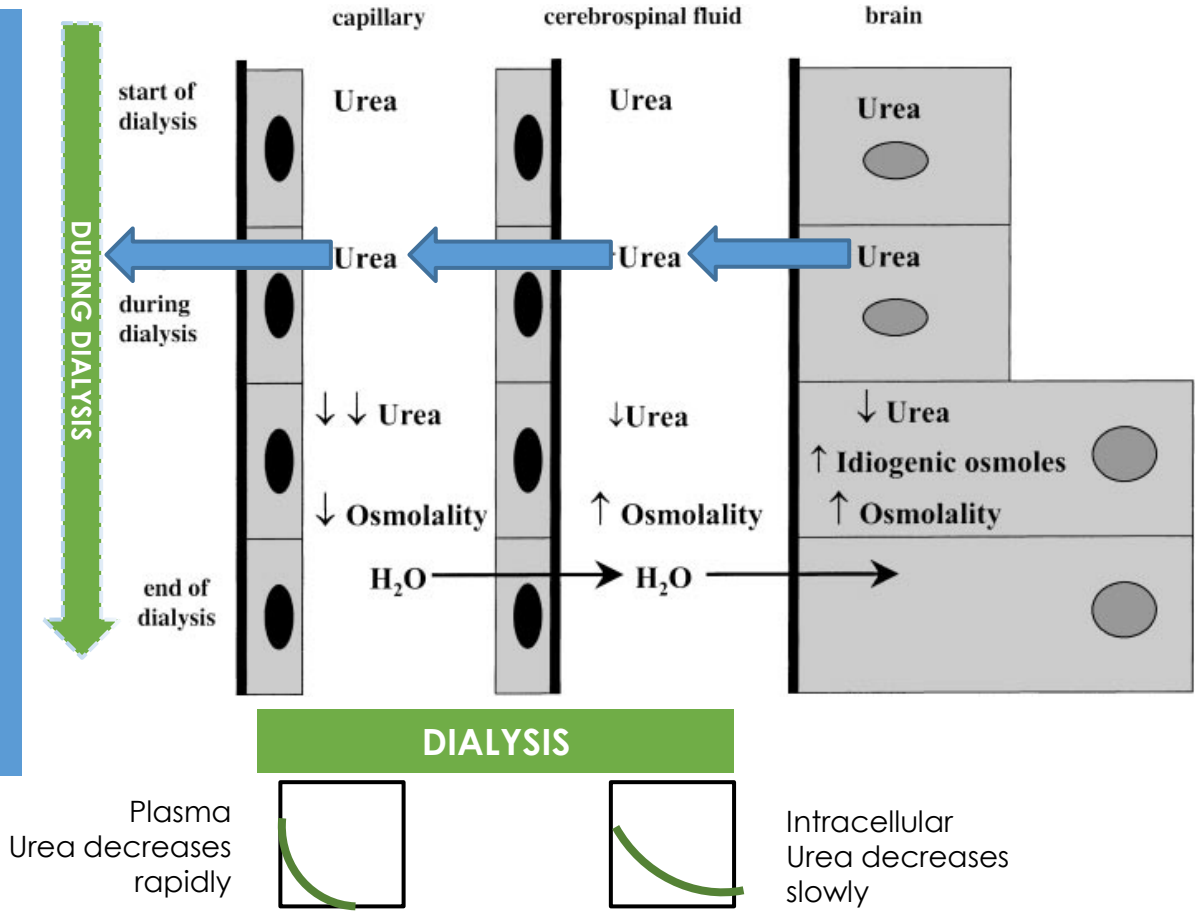
- Rationale is to reduce intracranial pressure following TBI, hemorrhage and stroke
- Manage severe hypo and hypernatremia
- Minimize dialysis diseqilibrium

Pathogenesis of Dialysis Disequilibrium Syndrome

- increased removal of plasma urea
- slower removal from CSF and brain tissue

-> osmotic gradient with passage of water from the relatively hypotonic plasma to the relatively hypertonic brain

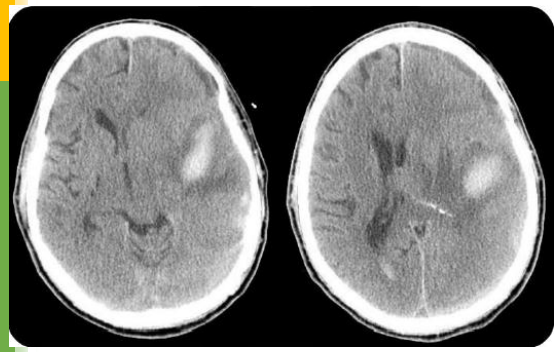
-> brain edema.



Clin Kidney J (2013) 6: 526–529

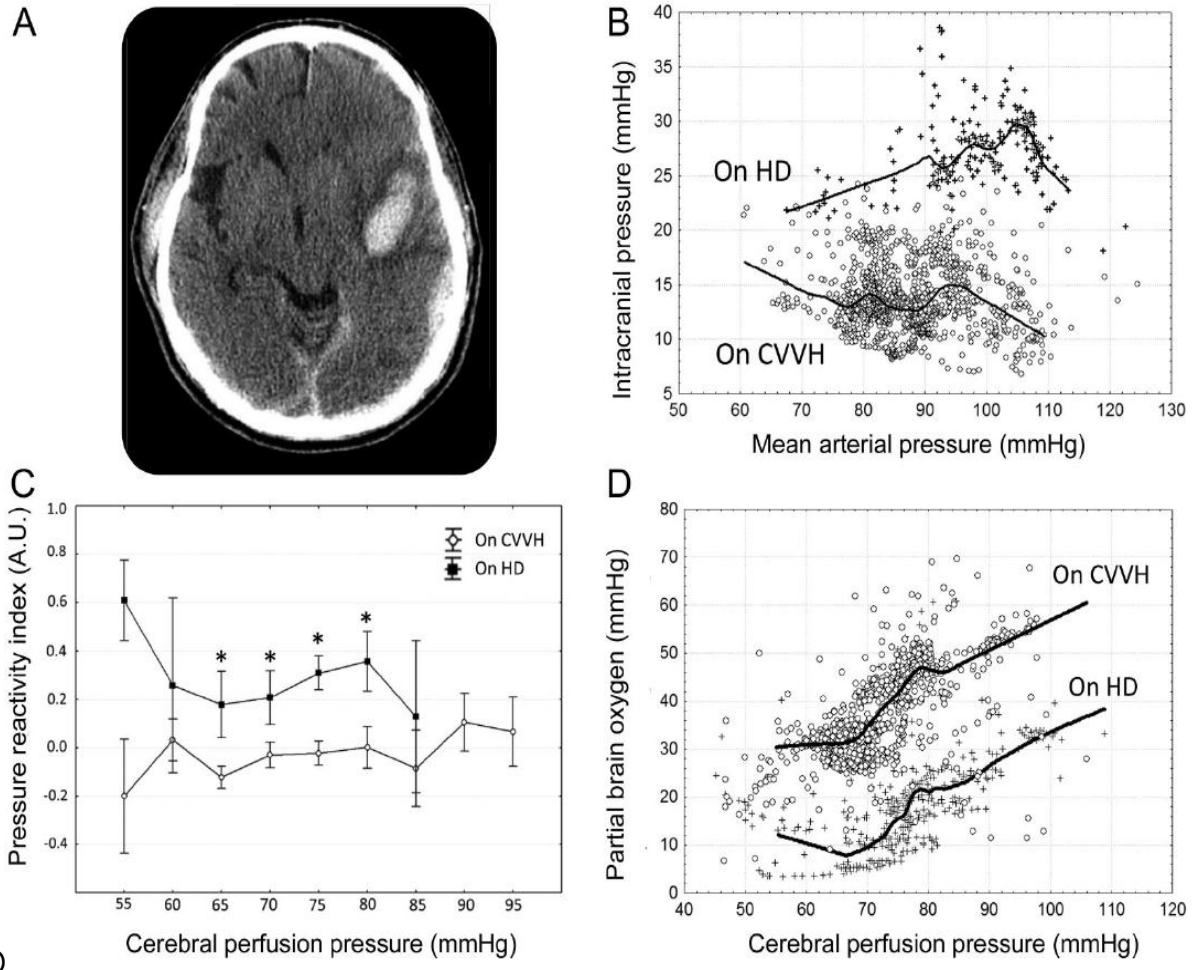
Intracranial Pressure CRRT vs. IHD

A 59-year-old man with HTN, type 1 diabetes, and ESRD on HD presented after head trauma from a fall while walking



Follow-up Head CT 14 days of IHD

Figure 1 Brain CT and physiologic data of the patient



Ko et al Neurology 2012;78:e36

CRRT for Neurological Support

Patients with intra cranial hypertension or cerebral edema

- *Autoregulation is lost!*
- Sudden changes in systemic or intra-abdominal pressure change intracranial pressure
  - Patients with abdominal compartment syndrome
- Patients with fulminant liver failure or acute decompensated liver cirrhosis

Patients with severe azotemia

- Correct azotemia *slowly,* to avoid dialysis dysequilibrium and worsened brain edema

Patients with hyponatremia

- Correct [Na]p *very slowly* to avoid osmotic demyelination syndrome
- Urea protects against osmotic demyelination syndrome

CRRT for Nutritional Support

Nutrition

- Create space for nutritional support fluids preventing fluid accumulation
- Provide adequate protein and calories
- Replenish vitamins and trace elements
- permits accurate assessment of nutritional needs and catabolic state

Protein losses with CRRT

- CAVHD
- AN-69 (0.43 m2; PAN membrane)
- BFR MAP dependent (80 mls/min)
- Qd @ 1 l/hr; Quf 340 mL/hr
  - AA losses = 9% of total intake
- Qd @ 2 l/hr; Quf 340 mL/hr
  - AA losses =12% of total intake

Davies et al, Crit Care Med, 1991

- CVVH and CVVHDF
- Polysulfone membranes
  - (Amicon 20 and Fresenius F-80)
- Qb 100-300 mls/min
- Qd 1000 ml/hr + 600 mL/hr UFR
- 1.2 - 7.5 gm/day of protein losses

Mokrzycki and Kaplan, *J Am Soc Neph* 1996

Amino acid and protein losses represent between 10-12% of total delivered nutritional proteins
Glutamine loss accounted for approximately 20% of total AA loss

Maxvold et al, Crit Care Med 2000;28(4):1161-5

CRRT for Thermal Regulation

Temperature

- Heat loss across circuit and filter
- Thermal control allows manipulation of core temperature
- Hypothermia reduces metabolic rate

Continuous Hemofiltration-Related Hypothermia: Influence on Gas Exchange in Sepsis

20 pts CAVH/CVVH , ARF d/t septic shock
Studied first 30 minutes, subsequent 48 hr CRRT

	Group A	Group B
n	*9*	*11*
Ultrafiltration rate ml/hr	*855 +/- 278*	*1468 +/- 293*
Core Temp Change (C)	*37.6 +/- 0.9*	*34.8 +/- 0.8 p < 0.001*
Hemodynamic variables		
VO_2 (ml/min/m2)	*141 +/- 22*	*112 +/- 22 p < 0.01*
Metabolic rate	*7.1% decrease*	*20% decrease*

- *Inverse relationship between ultrafiltration rate/core temperature and VO_2 in septic pts treated with CVVH/CAVH*
- *Potential beneficial effects in malignant hyperthermia, febrile hypermetabolic, catabolic states*

Matamis D. Intensive Care Med 1994;20:431-436

Calculation of Heat Loss in CRRT

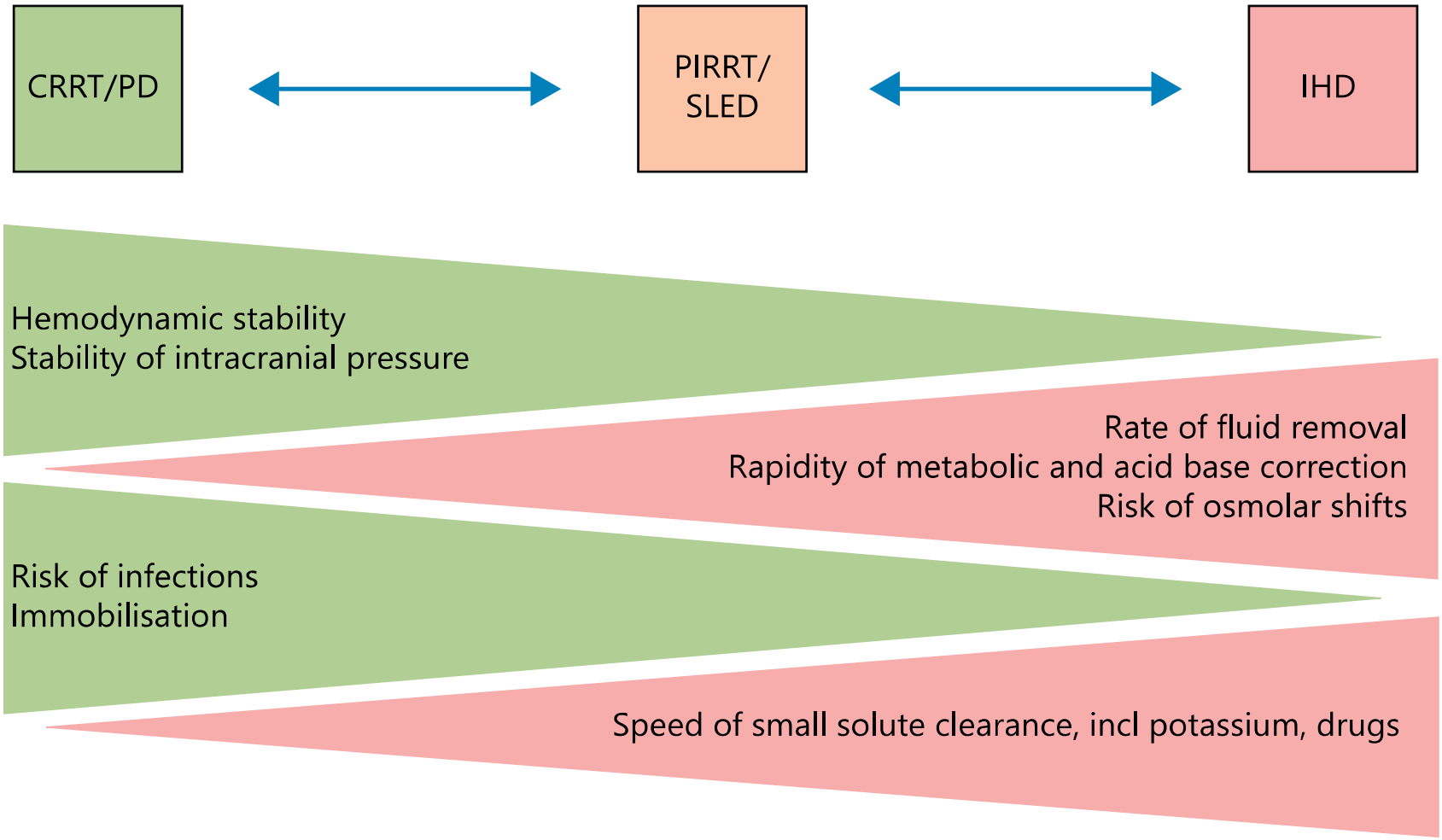
- Hypothermia associated with ↑ mortality
  - Dialysate is warmed by IHD machine
  - CVVHD: dialysate hung like IV bag at room temp
  - CVVH, CVVHDF: UFR solutions also hung like IV bags at room temperature
- Hypothermia is a common problem
  - 36 episodes of hypothermia
  - (core body temp <35.5 C) in 72 CRRT patients
    - *Yagi N et al. AJKD 1998;32:1023-30*

- *Manns M, et al. ASAIO J 1998:M601-5.*
  - Qb 120 mL/min Quf 1400mL/hr
- Heat loss = 765 kcal/d
  - blood tubing 26%
  - hemofilter 31%
  - produced UF 43%
- Heating UFR solution to 43 C↓ loss by 72%
- Take FRF /dialysate out of fridge!

Clinical Indications for CRRT

Organ Support	• Renal • Cardiac • Hepatic • Respiratory • Neurological • Nutrition • Thermal regulation
Disease modification	• Metabolic disorders • Drug Toxicity • Sepsis • Metastatic Cancer • Combination with apheresis

Patient Selection for Continuous Renal Replacement Therapy



Blood Purif 2016;42:224–237

CRRT When and How

CRRT Attributes → *Matching Therapy to Clinical Need* → *Prescription and Delivery*

Role of CRRT for renal support
How is it Done?

Prescription

- Machine PRISMAFLEX
- Filter HF-1000 filter set
- Mode: CVVHDF
- BFR: 100 ml/min
- Dialysate flow rate: 1000 ml/hr
- Patient fluid removal 1000 ml/hr
- Pre-filter replacement: 500 ml/hr
- Post-Filter dilution 200 ml/hr
- **Effluent volume 2700 ml/hr**

Post-filter replacement: to achieve target fluid balance

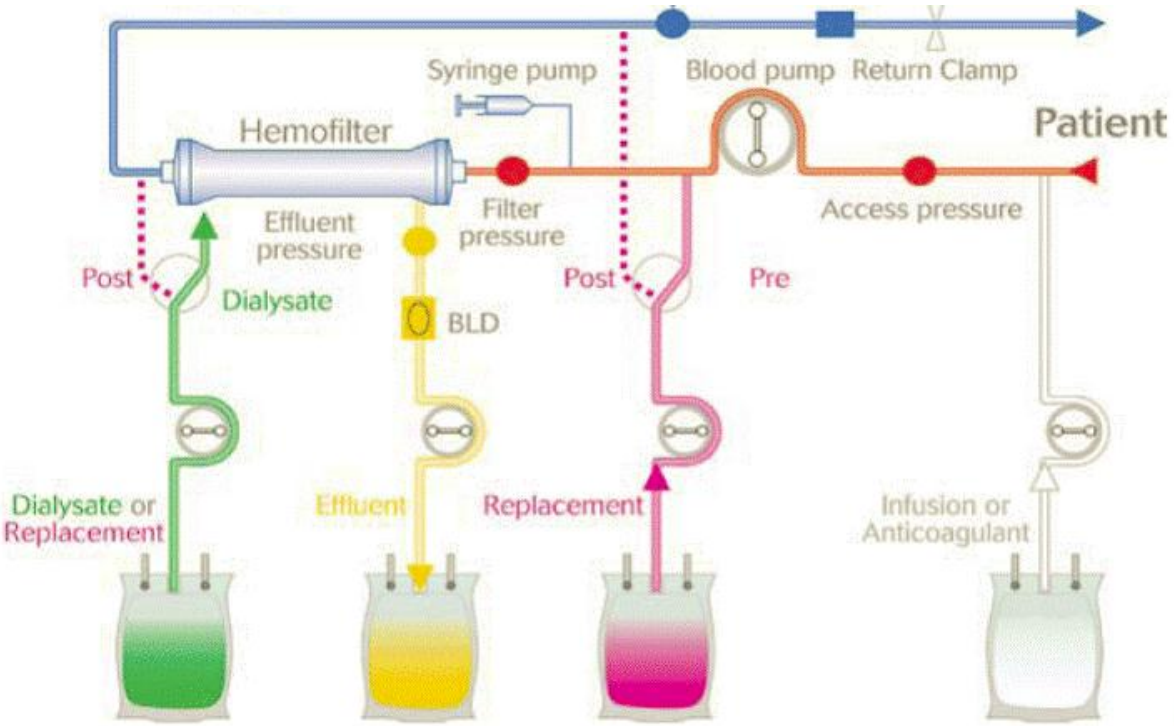
Anticoagulation: Regional citrate

- 4% tri-sodium citrate at 180 ml/hr
- Calcium chloride 40 ml/hr
- Monitoring: peripheral and post-filter ionized calcium

Solutions:

- Dialysate : Prismasate
- Pre-filter fluid: 0.9% saline
- Post-filter replacement: Prismasol or 0.9% saline b or or sterile water + 150 meq bicarb or 0.45% saline + 75 meq of bicarb

Hydraulic Circuit for PrismaFlex



Machine Programming Components:

Modality: CVVH, CVVHD, CVVHDF

Negative fluid balance desired (Fluid removal rate) (Fld)

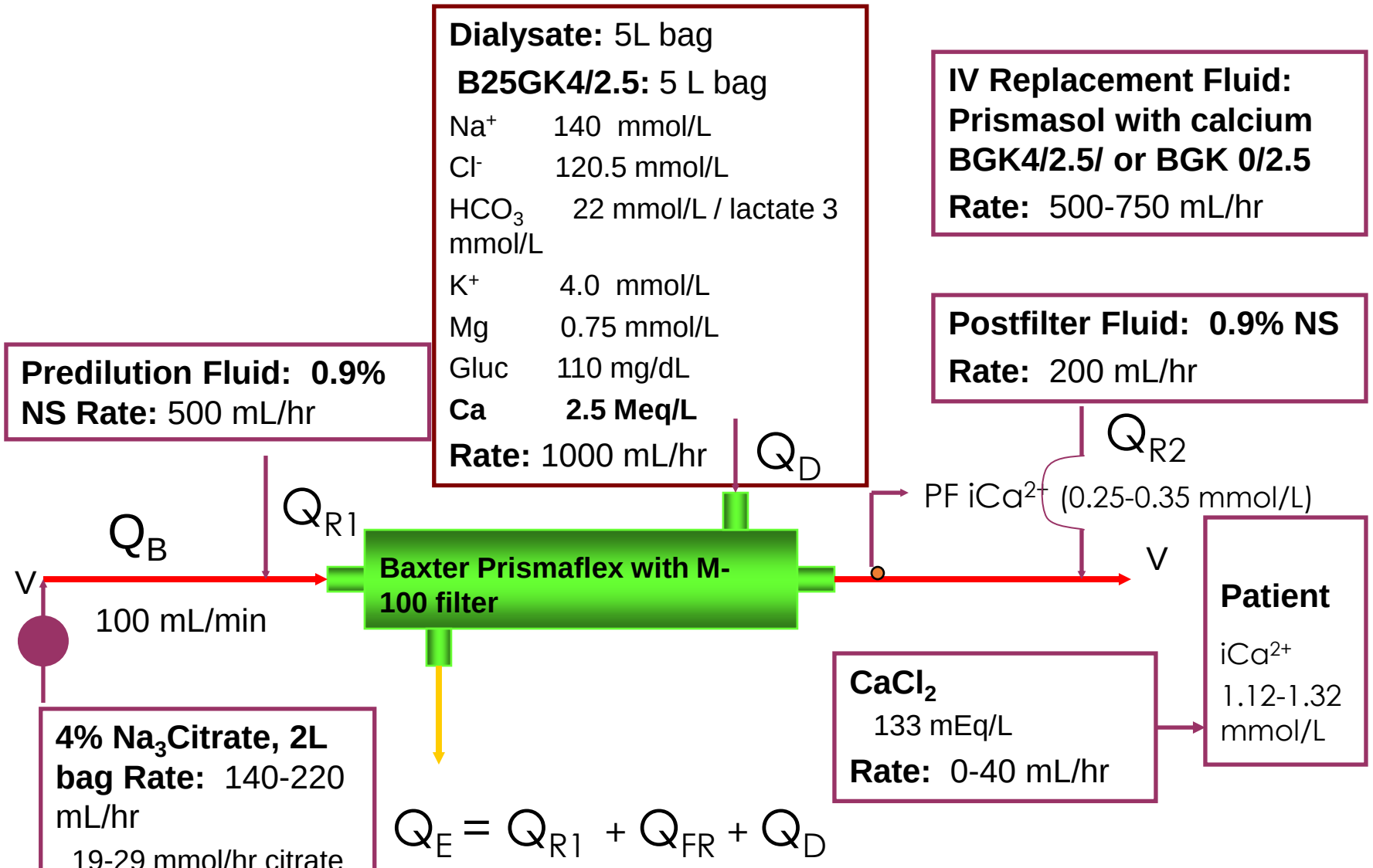
Replacement fluid pre vs post filter (RF)

Dialysate flow rate (DF)

Anticoagulant flow rate (AC)

Effluent Pump Speed = RF + DF + AC + Fld removal

San Diego Protocol (CVVHDF)**

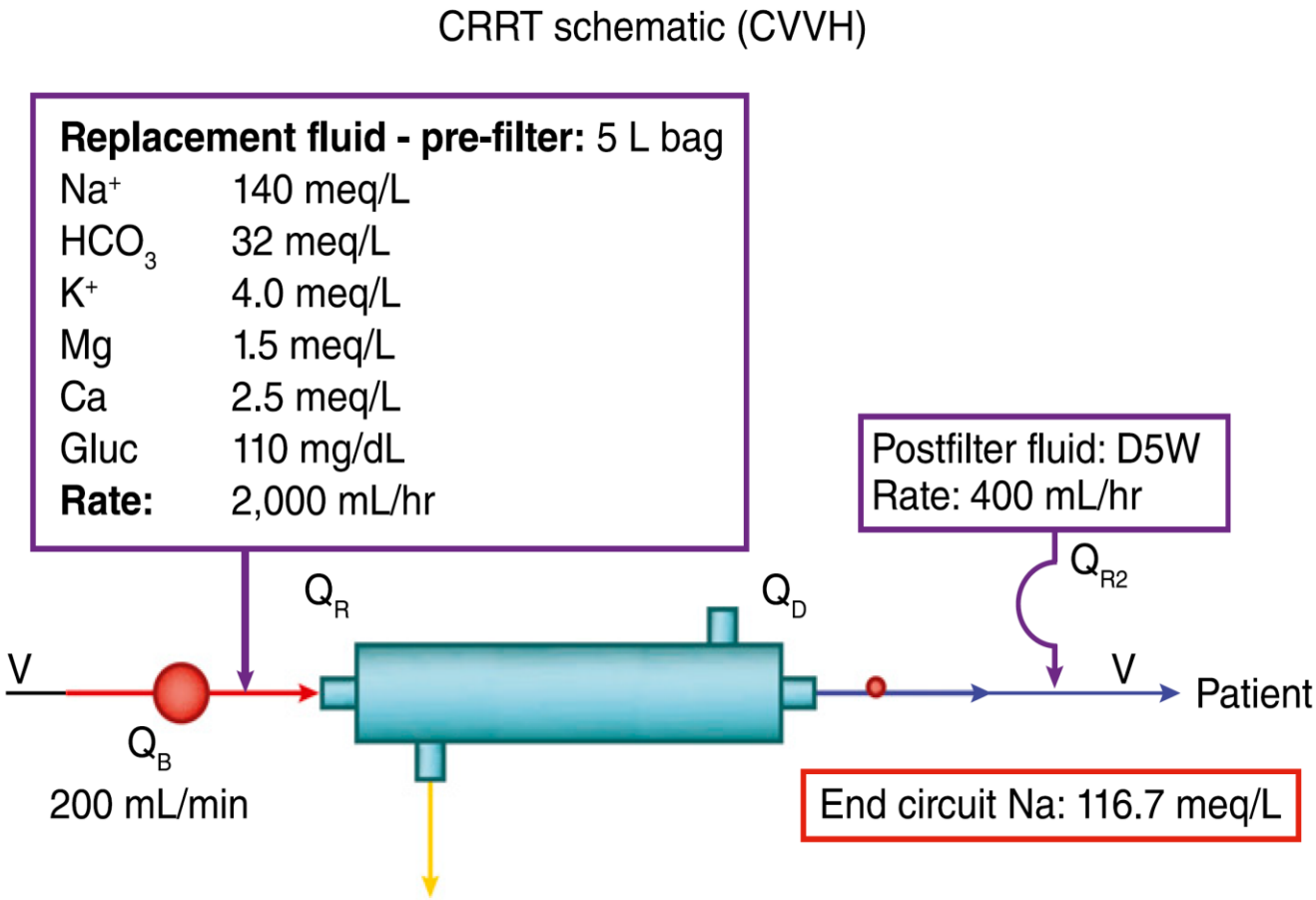


Av Filter life > 72 hrs

Commercial solutions

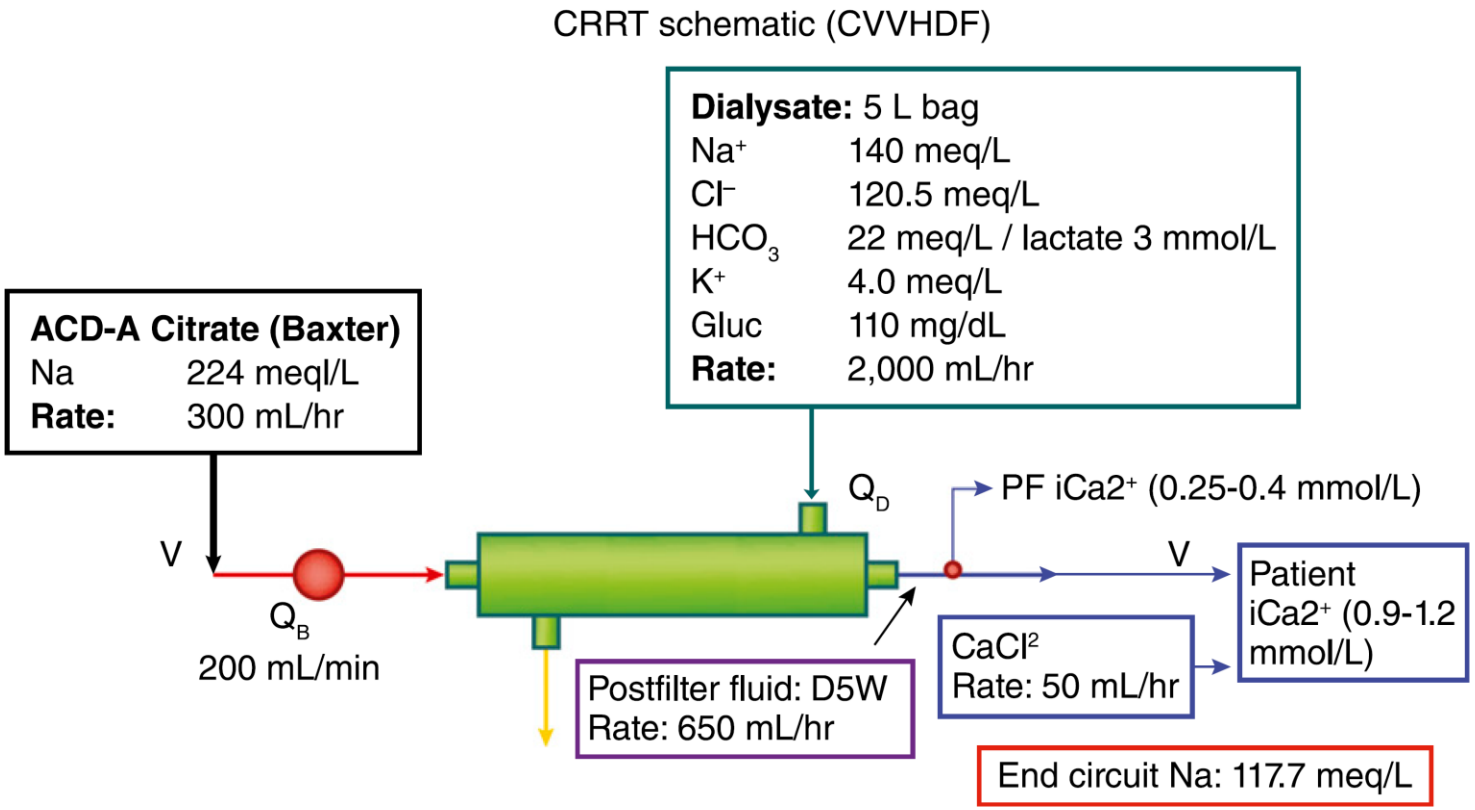
Mehta et al, KI, 1990 38(5): 976-981.

Management of Hyponatremia with CRRT Circuit Adjustments



Rosner et al : Clin J Am Soc Nephrol 2018. doi: https://doi.org/10.2215/CJN.13281117

Management of Hyponatremia with CRRT Circuit Adjustments



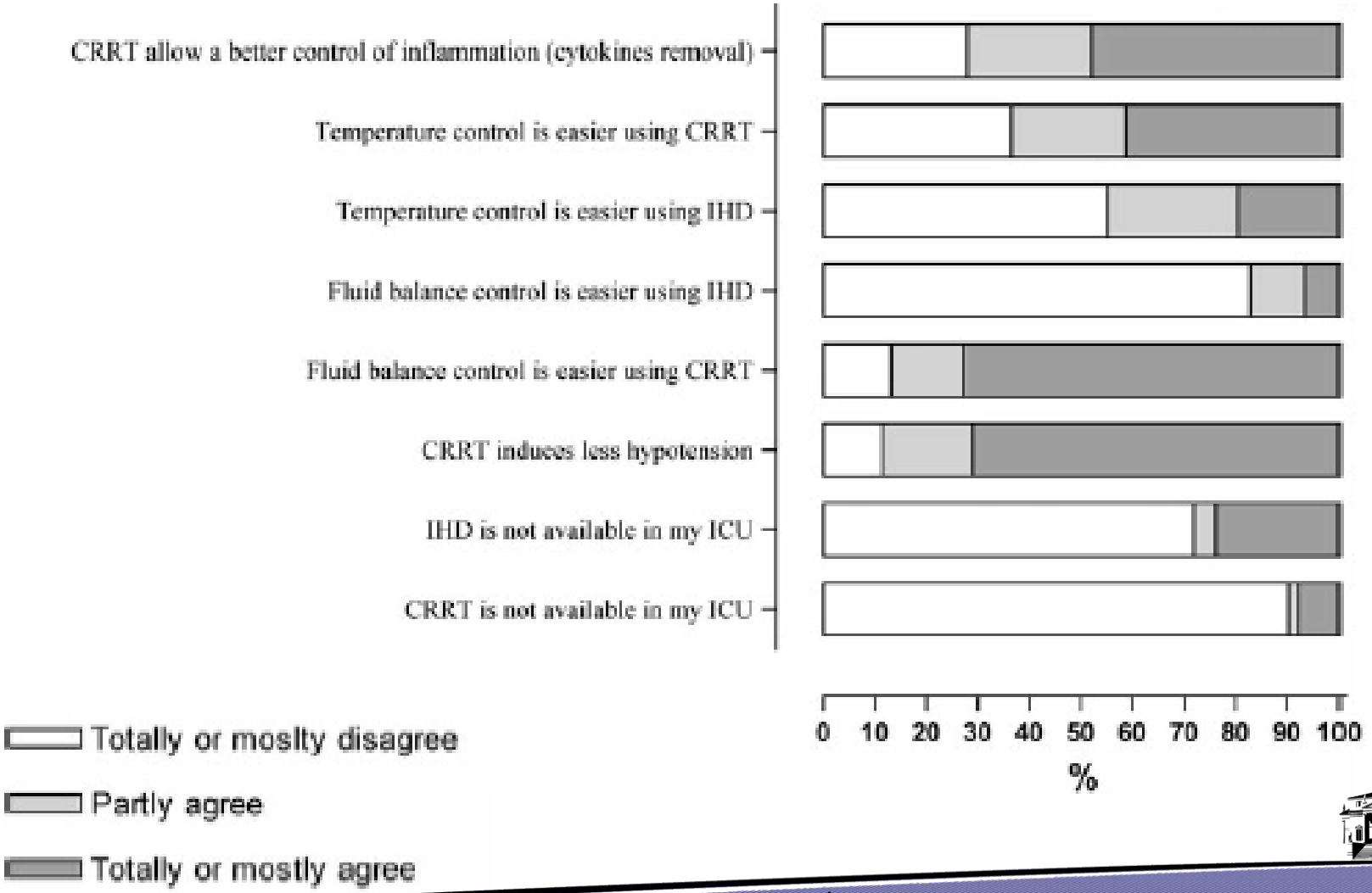
Rosner et al : Clin J Am Soc Nephrol 2018. doi: https://doi.org/10.2215/CJN.13281117

When Should We Not Use CRRT?

- Isolated AKI
- High clearances desired over short duration
- Mobility is desired
- Inadequate infrastructure
  - Machines and solutions
  - Nursing support
  - Untrained personnel
  - Protocols
  - Lab
  - Pharamacy

Management of renal replacement therapy in ICU patients: an international survey

(Legrand M et al: Intensive Care Med 2013;39:101-8)



When and How for CRRT Summary

CRRT operational characteristics facilitate its application for organ support

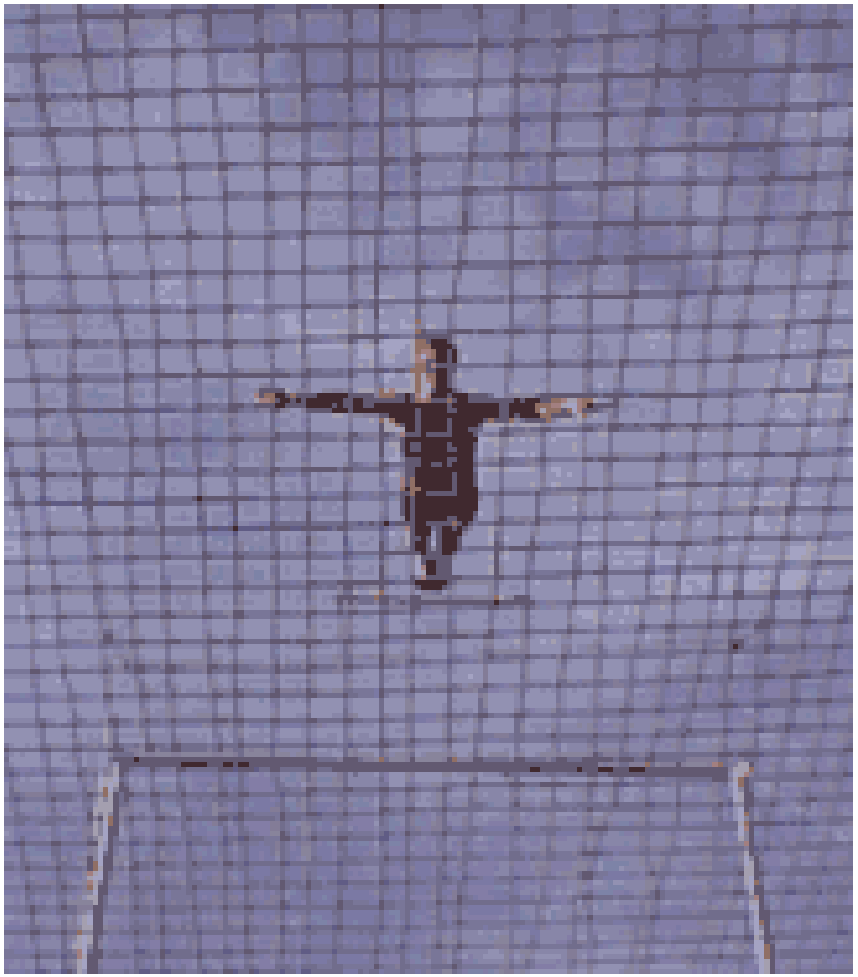
- Solute concentration can be manipulated independent of fluid balance
- Plasma composition can be altered by changing composition of dialysate and substitution fluid
- Fluid regulation can occur concurrently with solute removal to maintain patient fluid balance desired

Flexibility of this technique facilitates its use for a wide variety of indications

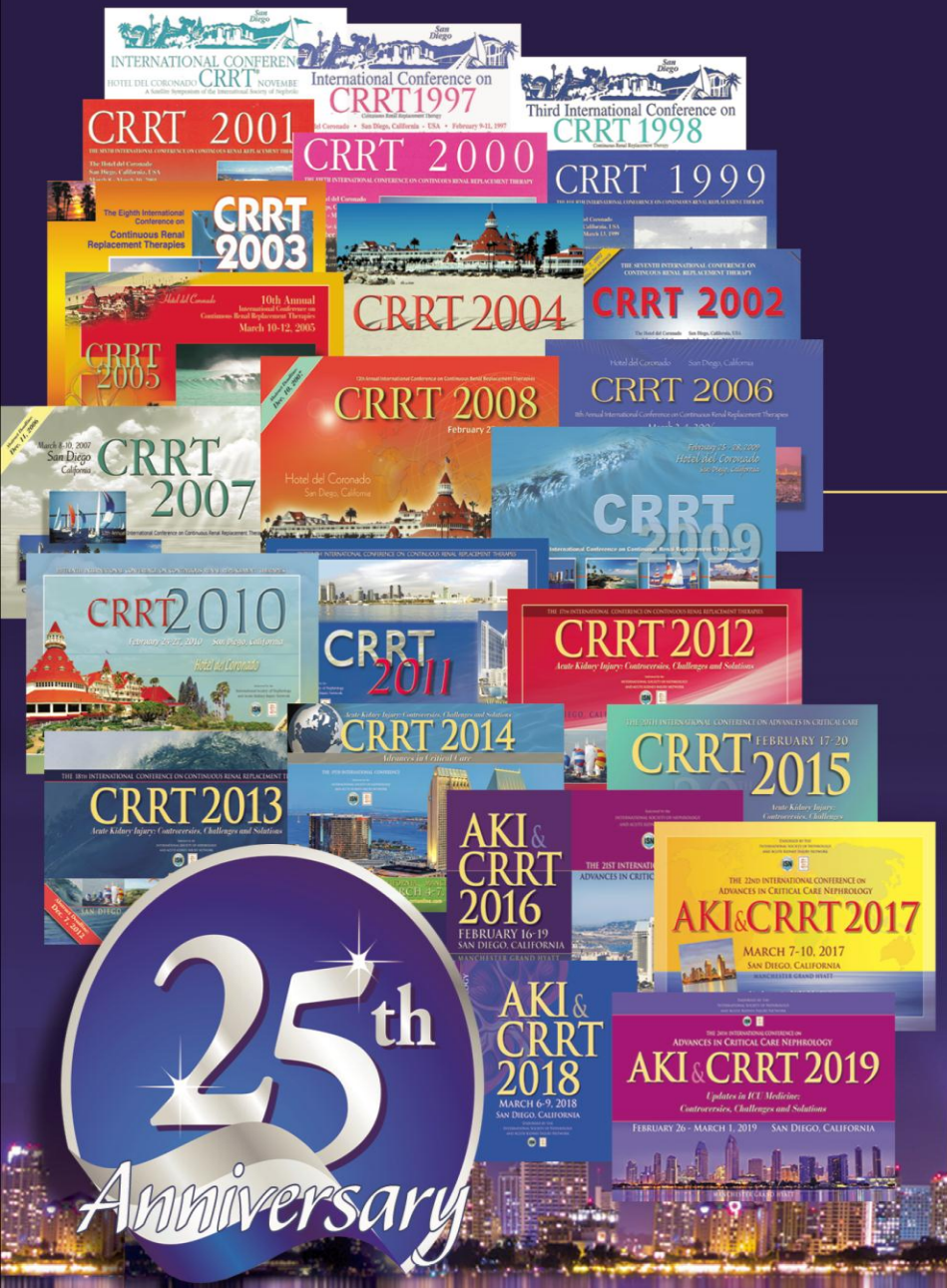
Goal should be to use modality for initial therapy in critically ill patients.

Further studies needed to assess effect on outcomes stratifying for timing of intervention, indication and dose.

Renal Replacement in the ICU



The CRRT Safety Net!



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Abstract Deadline: December 12, 2019