

ICU Nephrology and Continuous Renal Replacement Therapies

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Bio Slide



David Steele MD.

- Medical School: University of the Witwatersrand, Johannesburg, South Africa
- Residency: Penn State University Medical Center
- Fellowship: Massachusetts General Hospital
- Faculty: Harvard Medical School Assistant Professor
- Clinical: Clinical Director MGH Nephrology
- Interests: Acute Care Nephrology; CKD Transitions; ESRD Care

Conflict of Interest

Fresenius Medical Care

Dialysis Unit Medical Director

Acute Kidney Injury

Epidemiology

AKI Incidence/Prevalence

- AKI-EPI (Hoste et al. Lancet 2015):
 - AKI occurred in 57% of ICU patients
 - 13.5% of AKI patients required RRT
- FINNAKI Study (Vaara et al 2014)
 - 5.2% of all ICU admissions required RRT
 - Among AKI patients 18% required RRT

Mortality

- Mortality among ICU patients with acute kidney injury and multiorgan failure is high (~50%).

Cost

- Adjusted cost for hospitalization for patients requiring CRRT is substantial (Nursing; LOS; Consumerables)

RRT in ICU: Key Components

1. Vascular Access: Type and location
2. Type/Modality of RRT: iHD vs CRRT
3. Anticoagulation: Citrate vs Heparin
4. Initiation: Timing and Indications
5. Dose of Therapy: Effluent rate

Vascular Access in RRT for ARF

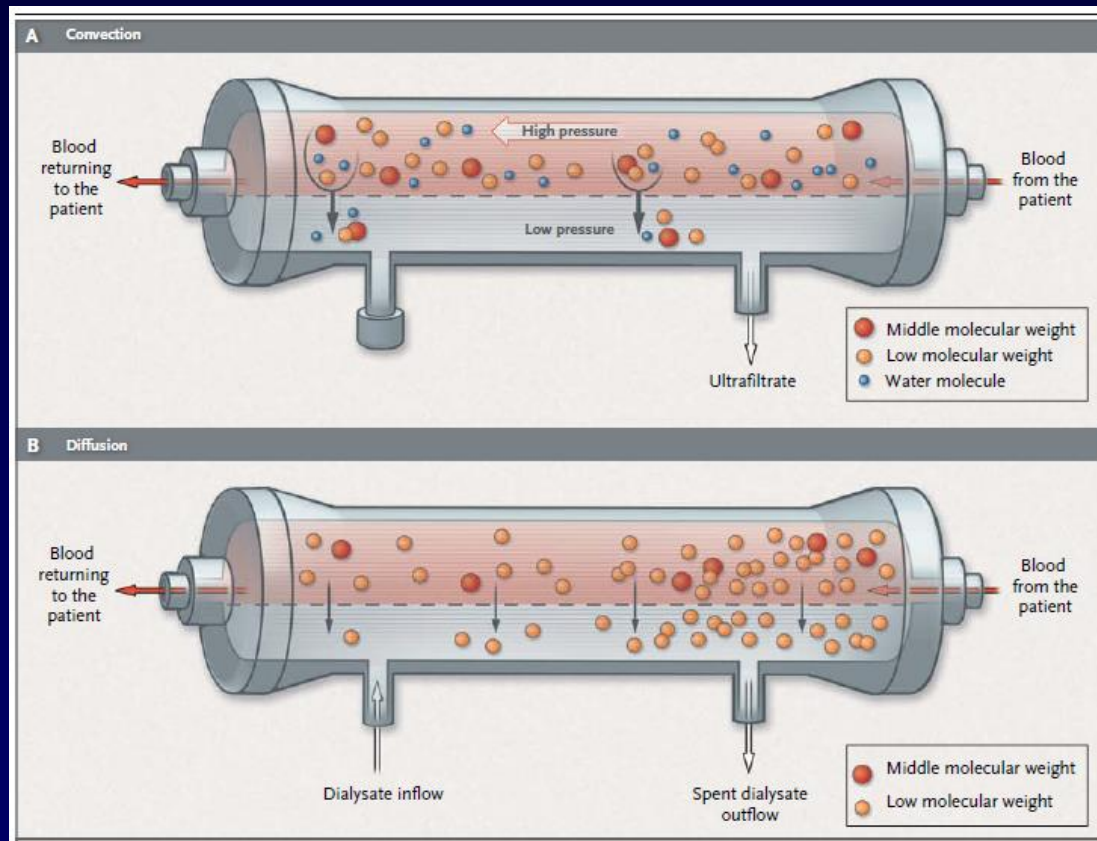
- An uncuffed non-tunneled dialysis catheter rather than a tunneled catheter should be used at the initiation of continuous renal-replacement therapy.
- The right jugular vein is the preferred choice. (Right femoral vein preferred to left internal jugular in some studies although not in obese patients)
- Ultrasonographic guidance is recommended.
- Patients with expectation of >2 weeks RRT requirement may be candidates for a tunneled HD catheter
- Nephrologists are placing vascular access on a less frequent basis than in the past
- Per ABIM: Procedural skill in vascular access placement must be provided at “an opportunity to train” standard by Nephrology Training programs



<http://www.nejm.org/doi/full/10.1056/NEJMvcm055053>

Basic principles of fluid and solute clearance in continuous renal replacement therapies

Solute transfer by Convection and Diffusion



Convection

- Solutes pass across a semipermeable membrane in association with the plasma water (ultrafiltrate) generated as a result of a transmembrane pressure gradient.

Diffusion

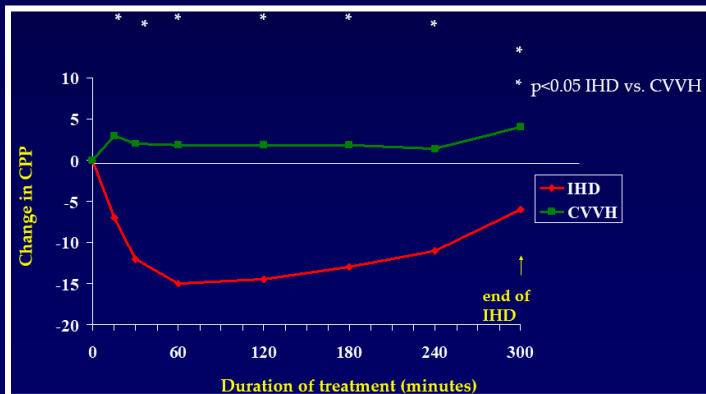
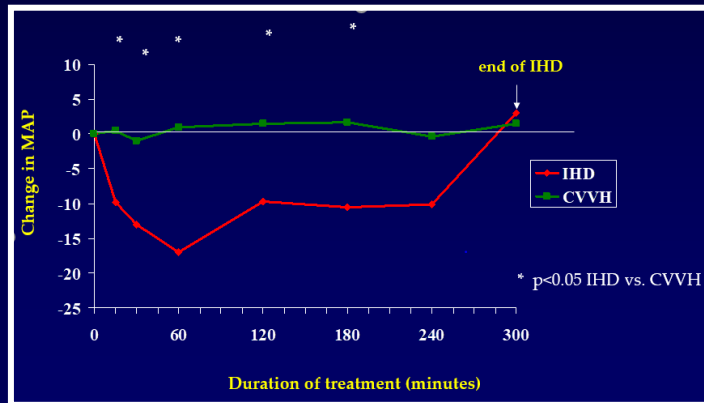
- Molecules in solution pass across a semipermeable membrane and move from regions of higher concentration to lower concentration as a result of concentration differences in dialysate

Intermittent vs Continuous RRT in Critically Ill Patients

- Selection of RRT modality should be individualized according to the patient's clinical and hemodynamic status.
- In patients who are hemodynamically unstable, CRRT rather than IHD is physiologically more appropriate.
- Caveat: IHD may be better than CRRT for removal of certain toxins and in severe hyperkalemia
- PD should be considered as a suitable RRT modality in AKI treatment in all settings

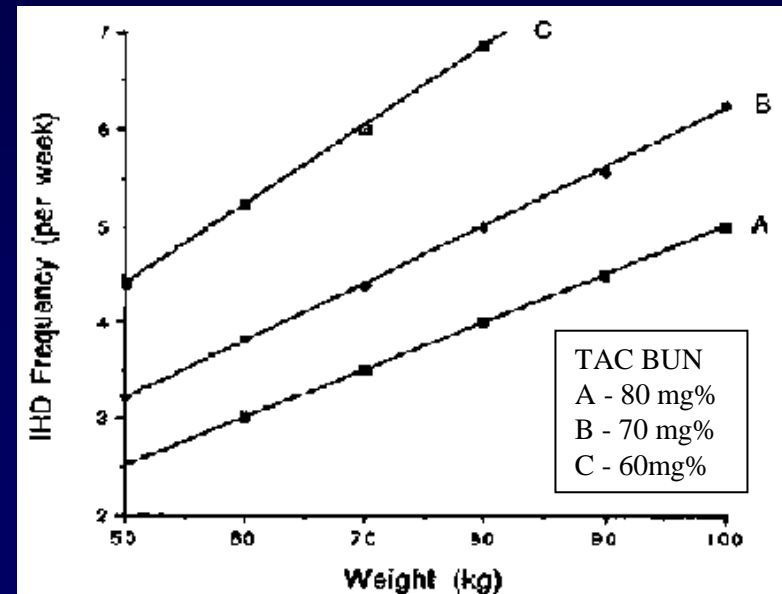
Intermittent vs Continuous RRT in Critically Ill Patients

Change in MAP and Cerebral Perfusion Pressure during dialytic support

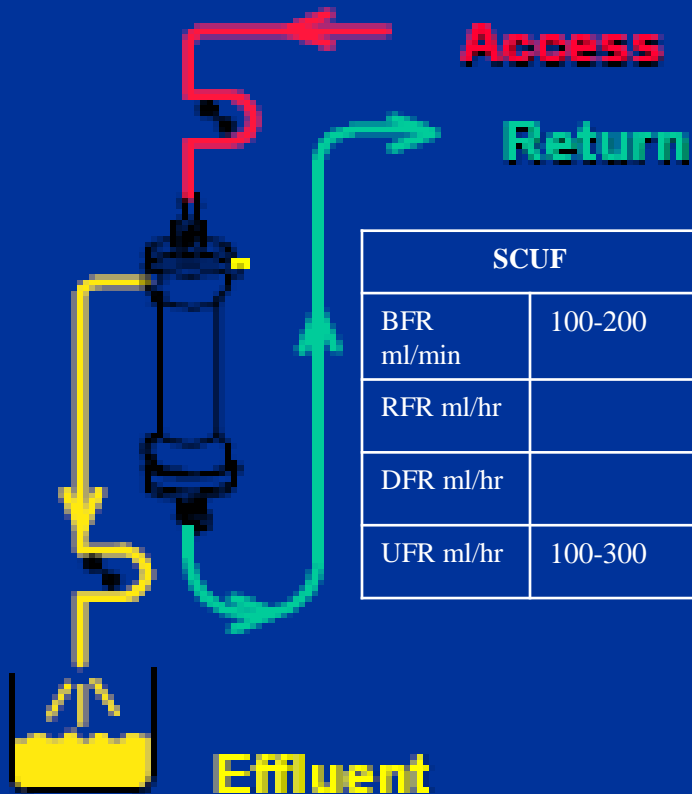


Hypercatabolic patients require increased BUN clearance:

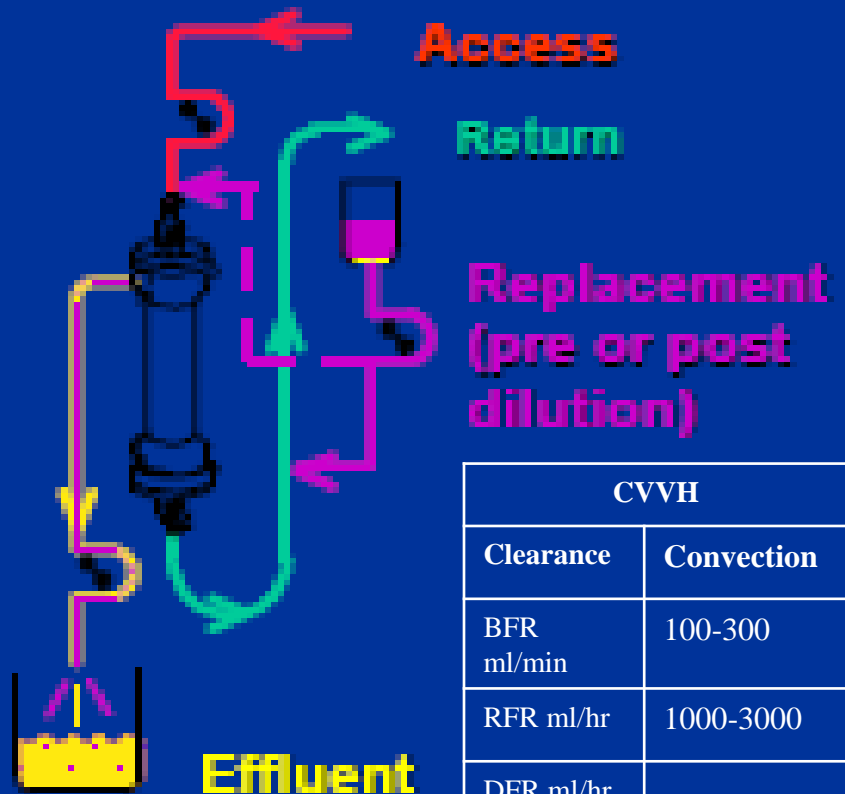
Predicted IHD frequencies for achieving desired time averaged BUN



CRRT Modalities

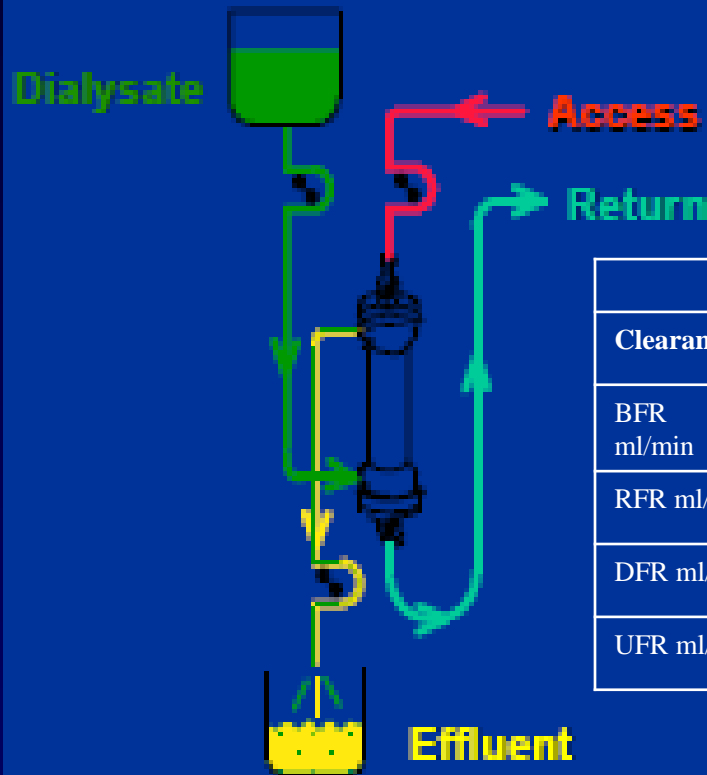


SCUF



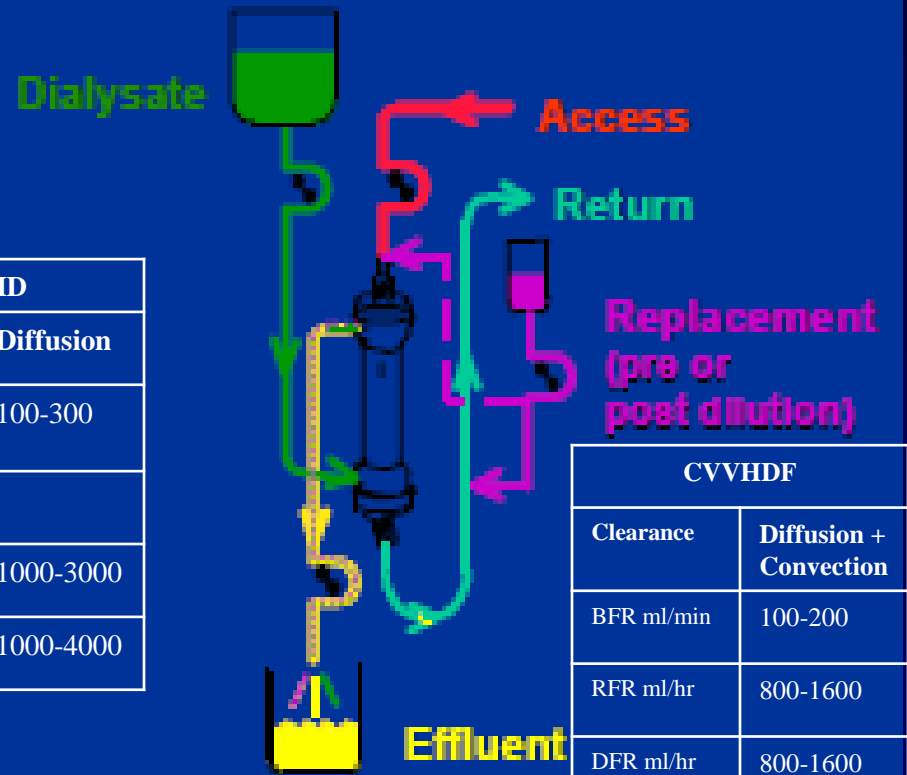
CVVH

CRRT Modalities cont...



CVVHD	
Clearance	Diffusion
BFR ml/min	100-300
RFR ml/hr	
DFR ml/hr	1000-3000
UFR ml/hr	1000-4000

CVVHD



CVVHDF	
Clearance	Diffusion + Convection
BFR ml/min	100-200
RFR ml/hr	800-1600
DFR ml/hr	800-1600
UFR ml/hr	1000-4000

CVVHDF

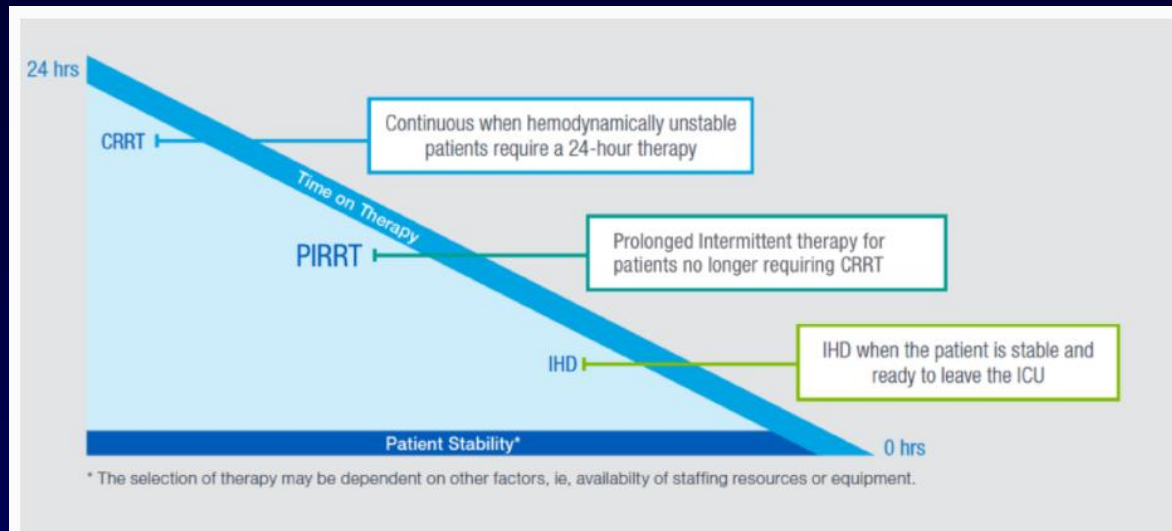
Retrospective Cohort Study: CVVH vs CVVHDF

- Data from 153 patients
- Mortality:
 - Hospital and 30-day mortality were similar in the CVVH and CVVHDF groups
- Length of Stay:
 - ICU and Hospital LOS longer in CVVHDF group (but not statistically significant)

Primary outcomes: Univariate and multivariate regression analysis

Outcome	CVVH	CVVHDF	Univariate analysis	Multivariate analysis*
Mortality at 30 days, n/n (%)	54/94 (57)	32/59 (54)	OR [†] 1.14 (95% CI 0.59 to 2.19); P=0.70	OR 1.35 (95% CI 0.62 to 2.95); P=0.45
Hospital mortality, n/n (%)	55/94 (59)	37/58 (64)	OR 0.80 (95% CI 0.41 to 1.57); P=0.52	OR 0.85 (95% CI 0.38 to 1.89); P=0.69
ICU length of stay, days, mean	19.35	46.84	MD [‡] -27.5 (95% CI -59.46 to 4.43); P=0.09	MD -28.22 (95% CI -65.26 to 8.81); P=0.14
Hospital stay, days, mean	28.53	62.85	MD -34.32 (95% CI -68.03 to -0.60); P=0.05	MD -34.14 (95% CI -72.92 to 4.65); P=0.08

Prolonged Intermittent Renal Replacement Therapy -PIRRT



iHD variant: Slow Low Efficiency Dialysis - SLED

- Standard iHD equipment
- Daily or 5-6 days a week (as opposed to qod)
- 6-8 hour treatment duration
- 200 ml/min BFR
- 300 ml/min DFR
- UF Rate 200-400ml/hr

CRRT variant: Accelerated Veno-Venous Hemofiltration - AVVH

- Replacement fluid rate largely determines clearance in CRRT
- Running CRRT at 1.6L/hr for 24 hour can be translated to 4-5L/hr over a 10 hour period of AVVH.
- Both cases results in ~ 40L/day of replacement fluid

Meta-analysis of PIRRT vs CRRT

- Twenty-one studies (RCT's or prospective cohort studies)
- Mortality:
 - CRRT *vs* IHD: RR 1.00 [95% CI, 0.92–1.09],
 - CRRT *vs* SLED: RR 1.23 [95% CI, 1.00–1.51])
- Dialysis dependence:
 - CRRT *vs* IHD: RR 0.90 [95% CI, 0.59–1.38]
 - CRRT *vs* SLED: RR 1.15 [95% CI, 0.67–1.99]).
- RRT modality (PIRRT *vs* CRRT) was not associated with in-hospital mortality or dialysis dependence

Anticoagulation for CRRT.

KDIGO Guidelines:

5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:

5.3.2.1: For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (1C)

5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)

5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (2C)

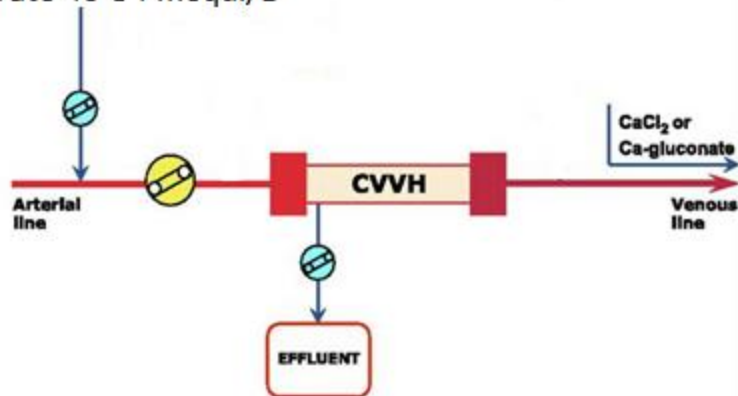
Anticoagulation for CRRT: Systemic Citrate

Citrate Replacement Solution

Na 130-140; K 0; Cl 100-105;

Mg 1.5 Ca 0

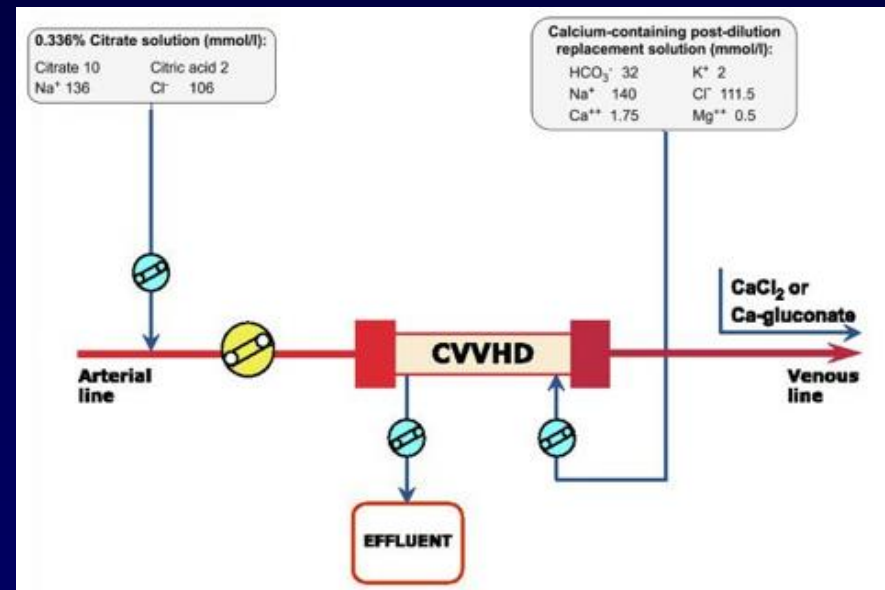
Citrate 40-54 mequi/L



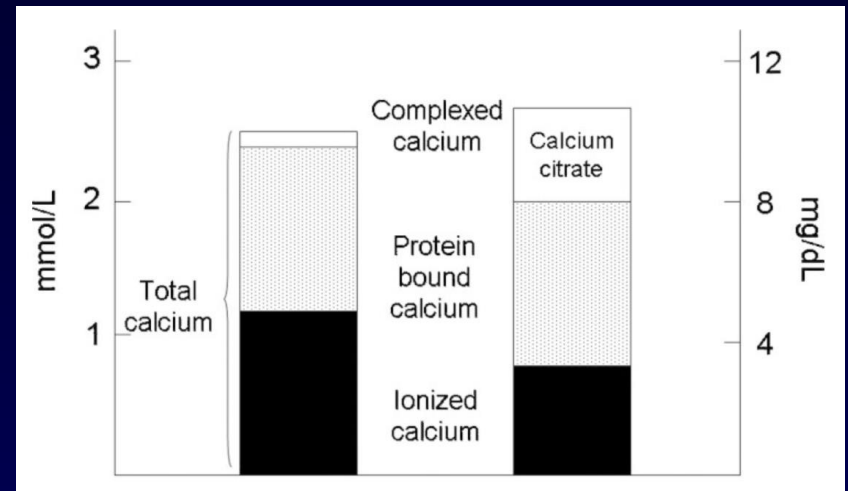
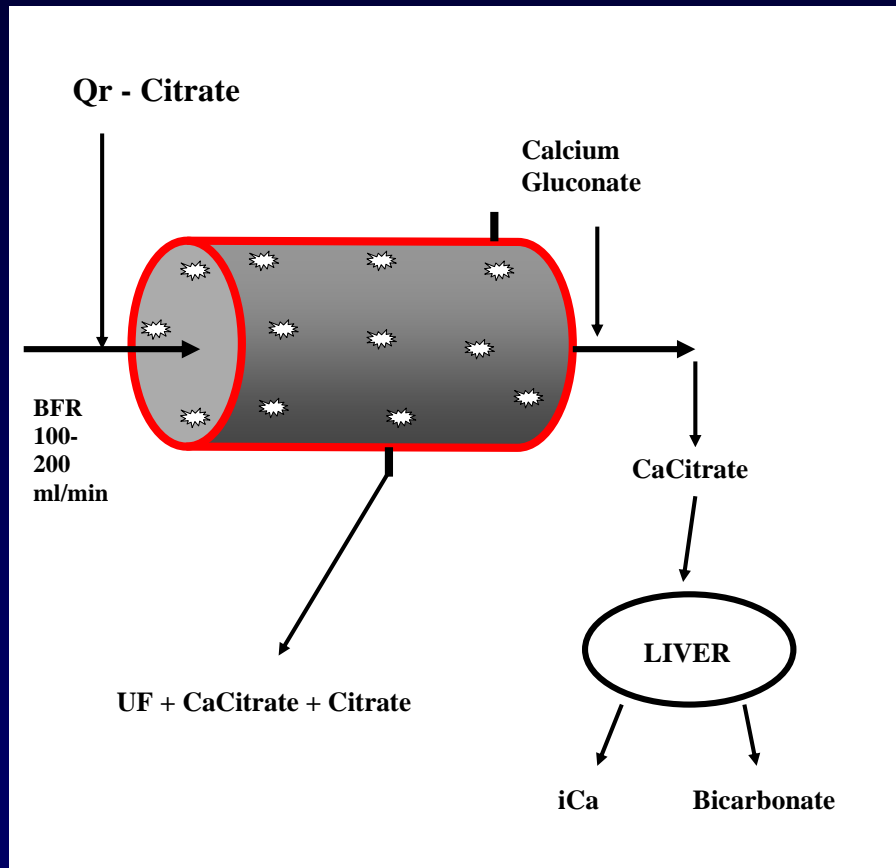
- Systemic Citrate based Replacement fluid
 - Citrate is an organic acid with a low molecular weight (298 daltons).
 - By chelating calcium, sodium citrate inhibits thrombin generation and prevents coagulation.
- Prefilter infusion
- BFR reduced in order to effect appropriate Citrate concentration per unit BFR
- Post filter or systemic IV Calcium infusion to reverse citrate coagulation effect

Anticoagulation for CRRT: Regional Citrate

- Citrate infusion rate is titrated to maintain $[iCa] \leq 0.35$ mmol/L within the filter to facilitate adequate anticoagulation.
- This corresponds to a blood citrate conc ~ 4 - 6 mmol/L in the circuit.
- BFR needs to be down titrated to 80-120/h/min in this context
- Due to risk of hypocalcemia IV $CaCl$ or $CaGluc$ is infused either at the end of the CRRT circuit or centrally.
- Postfilter, ionized and total calcium levels should be monitored
- The majority of the calcium-citrate complex is removed across the hemofilter and the remaining amount, infused into the patient, is rapidly metabolized to bicarbonate
- Citrate's half-life is ~ 5 minutes.



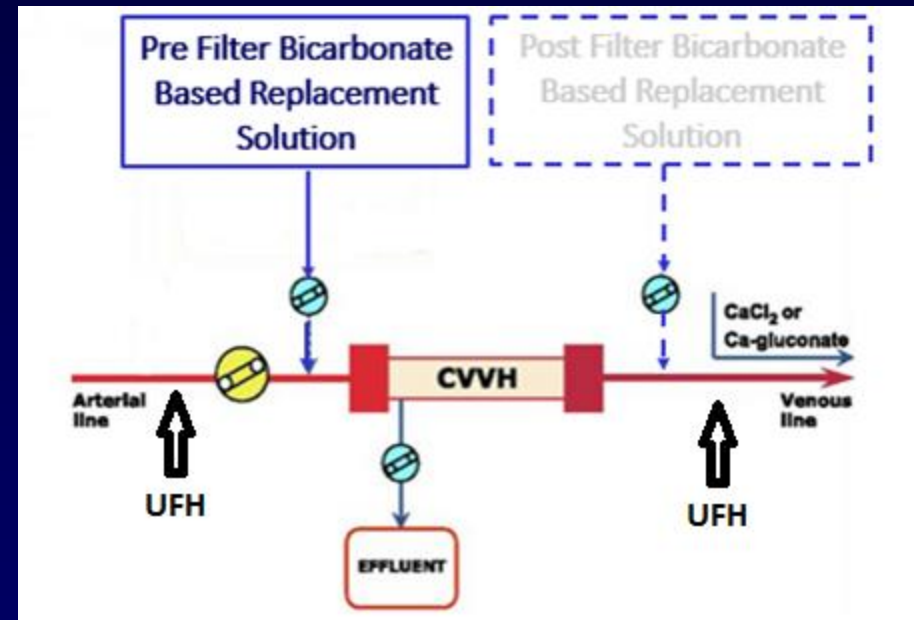
Citrate toxicity



- Low ionized Calcium
- Elevated total serum Calcium
- Exacerbation of serum acidosis
- Elevation of anion gap

Anticoagulation for CRRT: Systemic Heparin

- Limited to patients without bleeding complications or coagulopathy
- Low dose bolus
 - 500 to 1000u
- Therapeutic target:
 - PTT 1.5 normal (40-60)
 - target anti-factor Xa level 0.3-0.5 IU/mL



Regional Citrate vs Systemic Heparin

JAMA | Original Investigation

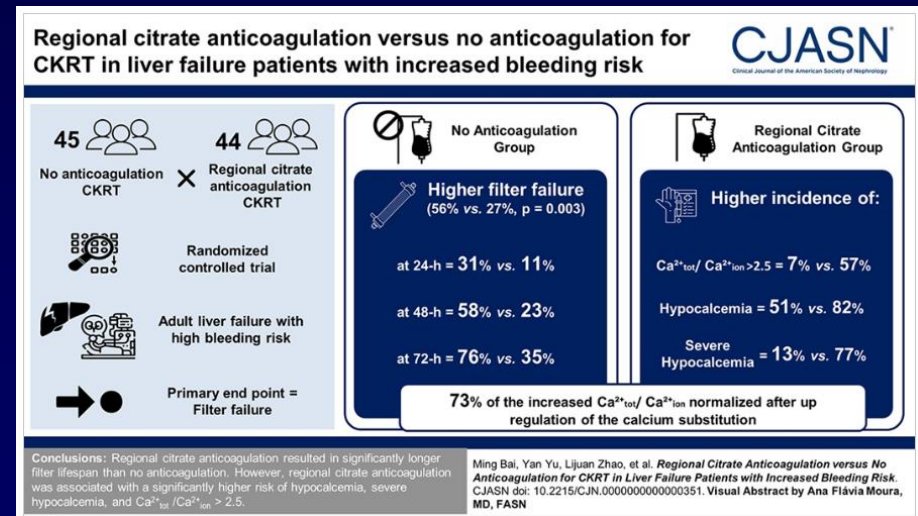
Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Life Span and Mortality Among Critically Ill Patients With Acute Kidney Injury
A Randomized Clinical Trial

- 26 German centers, 596 patients, ~75% surgical
- Citrate resulted in longer filter life (47 hours vs. 27 hours)
- No 90-day mortality difference (51.2% vs. 53.6%), though adjusted HR trended towards benefit with citrate (0.79 [0.63 to 1.004]; $p = .054$)
- Citrate: Less major bleeding (5.1% vs. 16.9%), more hypophosphatemia (15.4% vs. 6.2%) and hypocalcemia (1.4% vs. 0.3%)

Regional Citrate Anticoagulation versus No Anticoagulation for CKRT in Patients with Liver Failure with Increased Bleeding Risk

Bai, Ming¹; Yu, Yan¹; Zhao, Lijuan¹; Tian, Xiujuan¹; Zhou, Meilan¹; Jiao, Jing¹; Liu, Yi¹; Li, Yajuan¹; Yue, Yuan¹; Wei, Lei¹; Jing, Rui¹; Li, Yangping¹; Ma, Feng¹; Liang, Ying²; Sun, Shiren¹

- For patients with liver failure with a higher bleeding risk who required CKRT, regional citrate anticoagulation resulted in significantly longer filter lifespan than no anticoagulation.
- Regional citrate anticoagulation in patients with liver failure was associated with a significantly higher risk of hypocalcemia, severe hypocalcemia, and $\text{Ca}^{2+}_{\text{tot}}/\text{Ca}^{2+}_{\text{ion}} > 2.5$.



CRRT Replacement Solutions Available Worldwide

Components	Citrate-free Solutions					Citrate-containing Solutions					
	PrismaSol BGK, B22GK, or BK	PrismaSATE BGK, B22GK, BK, or BzK	Phoxillum BK or B22K	PureFlow B RFP 400-456	Duosol 4551-4556	4% Sodium Citrate	ACD-A	Regiocit	Prismocitrate 10/2	Prismocitrate 18/0	Citra-HF Pre
Na ⁺ , mEq/L	140	140	140	130 or 140	140 or 136	408	225	140	136	140	139.9
K ⁺ , mEq/L	4, 2, or 0	4, 2, or 0	4	4, 3, 2, or 0	4, 2, or 0	—	—	—	—	—	3
Ca ⁺⁺ , mEq/L	0, 2.5, or 3.5	0, 2.5, or 3.5	0 or 2.5	0, 2.5, or 3	0 or 3	—	—	—	—	—	—
Mg ⁺⁺ , mEq/L	1, 1.2, or 1.5	1, 1.2, or 1.5	1.5	1 or 1.5	1 or 1.5	—	—	—	—	—	0.5
HCO ₃ ⁻ , mEq/L	32 or 22	32 or 22	32 or 22	35 or 25	35, 32, or 25	—	—	—	—	—	—
Lactate, mEq/L	3	3 or 0	—	—	—	—	—	—	—	—	—
Cl ⁻ , mEq/L	108-120.5	108-120.5	114.5 or 122	108.5-120.5	107.5-117	—	—	86	106	86	104
Dextrose, mg/dL	100 or 0	110 or 0	—	100	100 or 0	—	2,230	—	—	—	90
Trisodium citrate, mmol/L	—	—	—	—	—	136	75	18	10	18	13.3
Citric acid, mmol/L	—	—	—	—	—	—	38	—	2	—	—

- No citrate formulation is currently approved by the US Food and Drug Administration for CRRT anticoagulation, and as such use is considered off-label.
- Phosphate repletion is frequently required:
 - Severe hypophosphatemia can induce a variety of complications (muscle weakness, rhabdomyolysis, and myocardial depression).
 - CRRT-induced hypophosphatemia has been associated with prolonged mechanical ventilation or an increased need for tracheostomy.
 - Although data proving that prevention of hypophosphatemia improves outcomes are lacking, measures to mitigate CRRT induced hypophosphatemia are recommended.

Filtration Fraction

$$\text{FF} = [\text{Ultrafiltration Flow Rate}] / [\text{Plasma Water Flow Rate}]$$

Plasma Water Flow Rate = Blood flow rate x (1-hematocrit) + the prefilter replacement fluid flow rate + any other pre-pump infusion rate

- Target FF < 20%
- Higher fractions are associated with increased circuit clotting,
 - Causes hemoconcentration and blood protein-membrane interactions within the hemofilter
- A lower filtration fraction can be maintained by:
 - Keeping the ultrafiltration flow rate low
 - Increasing blood flow rate (which determines plasma water flow rate); limited by catheter function
 - Using prefilter replacement fluid in CVVH or CVVHDF

CRRT Dose:

KDIGO AKI Recommendations

Regarding Dose in CRRT

- 5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)
- 5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI (*1A*). This will usually require a higher prescription of effluent volume. (*Not Graded*)

CRRT Dosing: Clearance Equations - Delivered Dose

Recommended dose: Kt/V 3.9 per week

CVVH, CVVHD, and CVVHDF postfilter dilution

$$\text{StdKt/V} = Q_{\text{ef}} \times [10.080 / (W \times 0.55)] \times S$$

CVVH and CVVHDF prefilter dilution

$$\text{StdKt/V} = Q_{\text{ef}} \times [Q_{\text{bw}} / (Q_{\text{bw}} + Q_{\text{s}})] \times [10.080 / (W \times 0.55)] \times S$$

Q_{ef} – Effluent flow rate

W – Body weight

Q_{bw} – Plasma flow rate, calculated as Q_b(1 – hematocrit)

Q_s – Replacement fluid rate

S – Sieving coefficient

CRRT Dosing: Comparison of Studies

Study	Study type and Size	Intervention (dose estimated by effluent flow rate)	Outcome (Mortality)
Ronco Lancet 2000;356:26-30	Single Center RCT N 425	20cc/kg/hr vs 35cc/kg/hr vs 45cc/kg/hr (Post Filter CVVH)	59% vs 43% vs 42% 15d mortality: lowest dose with highest mortality p<0.005
Bouman Crit Care Med 2002;30(10):2205-11	Two Center RCT N 106	3-4L/hr vs 1-1.5L/hr (early start) vs 1-1.5 L/hr (late start)	72% vs 69% vs 75% (28d; NS)
Saudan KI 2006;70(7):1312-7	Single Center RCT N 206	CVVH (1-2.5 l/hr RF) or CVVHDF (1-2.5 l/hr RF+1-1.5 l/hr dialysate)	34% vs 59% (90D; P<0.05)
Tolwani JASN 2008;19(6):1233-8	Single Center RCT N 200	17cc/kg/hr vs 29cc/kg/hr (Pre Filter) CVVHDF	49 vs 56% (ICU discharge or 30d; NS)
VA Cooperative: ATN NEJM 2008;359(1):7-20	Multi Center RCT N 1124	35cc/kg/hr or 6 Qweek SLED or iHD vs 20 cc/kg/hr or TIW SLED or iHD (Prefilter CVVHDF)	46 vs 48% (60d; NS)
RENAL NEJM 2009;361(17):1627 - 38	Multi Center RCT N1508	40cc/kg/hr vs 25cc/kg/hr (CVVHDF post filter)	55% vs 55% (90d; NS)

Initiation of CRRT:

Guidelines re Timing of RRT in AKI

KDIGO

- Initiate RRT emergently when life threatening changes in fluid, electrolyte and acid base balance exist (*not graded*)
- Consider the broader clinical context, the presence of conditions that can be modified with RRT and the trends of laboratory tests – rather than single BUN and Creat threshold alone – when making the decision to start RRT (*not graded*)

ADQI

Consensus statement 17th Conference on CRRT

- Acute RRT should be considered when metabolic and fluid demands exceed total kidney capacity
- Not based solely on renal function or AKI stage
- RRT Initiation based on ability of kidney to meet demands

Timing of Acute RRT - Definitions

EARLY or PRE-EMPTIVE

- Start at an early stage of AKI (KDIGO stage 2 or 3)
- Goal: prevent development of life threatening complications of AKI

CONVENTIONAL or LATE

- Life threatening indications:
 - Acute hyperkalemia (i.e. > 6)
 - Severe acidemia ($\text{pH} < 7.15$)
 - Life threatening volume overload
 - inability to oxygenate
 - pulmonary edema
 - Uremia

Early Start vs Late Start RRT for AKI

Early Start Advantages

- Metabolic control
 - K control
 - Acid Base regulation
- Volume Control
 - Avoid Pulmonary Edema
- Potential Improved clinical outcomes
 - Mortality
 - ICU LOS

Early Start Disadvantages

- Access
 - Mechanical, bleeding, ID complications
- Dialysis
 - Clotting and blood loss
 - Hemodynamic perturbation
- Renal
 - Delayed spontaneous recovery
- Logistical
 - Cost and manpower

Early vs Delayed Start RRT Trials

Trial	Population	Result	Comment
ELAIN JAMA 2016 May 24-31;315(20):2190-9	231 pts. AKI KDIGO 2; <ul style="list-style-type: none"> Early: within 8hrs of AKI KDIGO 2 Delayed: within 12hrs AKI KDIGO 3 94.8% Surgical 	Mortality <ul style="list-style-type: none"> 39.3% early; 54.7% delayed. 	Early showed lower 90 day Mortality Predominantly surgical patients
AKIKI N Engl J Med 2016;375:122-33	Stage 3 AKI; 620 patients <ul style="list-style-type: none"> 79.9% Medical 	150 deaths among 311 patients early start 153 deaths among 308 patients late start 151 patients in late start group did not get HD	No significant difference in mortality Delayed start averted RRT in some patients Early start increased risk of infections
IDEAL N Engl J Med 2018;379:1431-42	488 pts randomized <ul style="list-style-type: none"> 100% Mixed sepsis 	58% early start; 54% late start died (P=0.38) 38% of pts in late group did not receive RRT 17% in the delayed group received emergent RRT	In patients with septic shock and AKI there was no significant difference in outcome for early vs late CRRT initiation
START AKI N Engl J Med 2020;383:240-51.	3019 randomized 2927 included: <ul style="list-style-type: none"> 1418 early start 903 standard start Mixed sepsis/Surgical 	Mortality: 43.9% early 43.7% standard (NS)	Accelerated (early) RRT <ul style="list-style-type: none"> No risk reduction in death at 90 days RRT dependence 10.4% vs 6% Shorter ICU stay

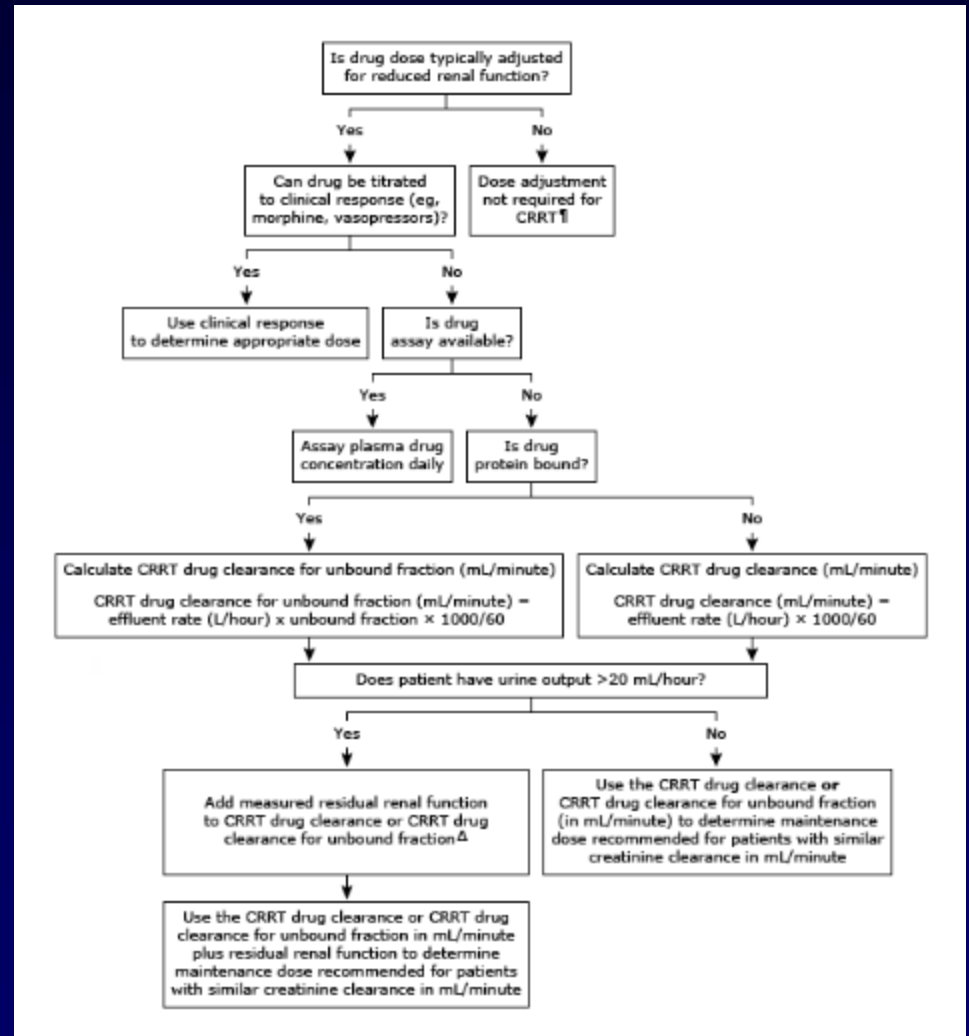
Peritoneal Dialysis in AKI (D)

- There is renewed interest in PD in AKI particularly in resource limited environments
- The 2020 International Society of Peritoneal Dialysis (ISPD) guideline suggested PD should be considered a suitable RRT modality for AKI treatment in all settings.
- The method of catheter implantation should be on the basis of patient factors and locally available skills.
- Bicarbonate solutions can be used in preference to Lactate based solutions in patients with liver impairment or lactic acidosis.

Drug Dosing in CRRT

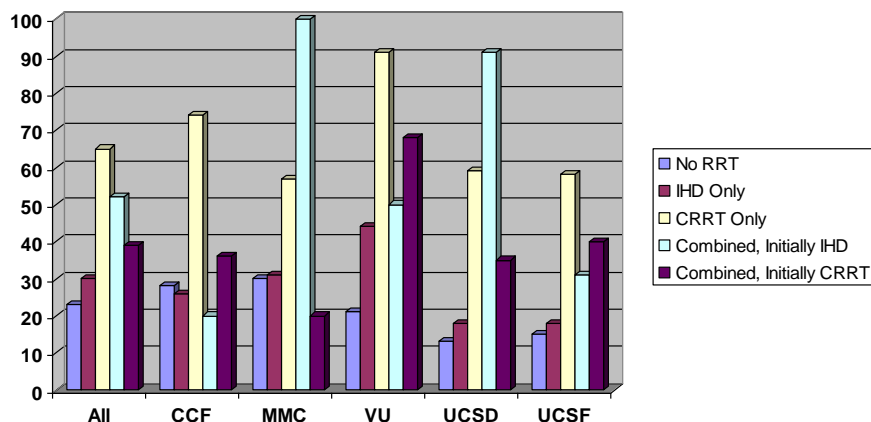
Removal of drugs by CRRT is complex involving:

- Factors affecting the patient
 - Volume overload
 - Shock and organ perfusion
- Drug characteristics
- Variable pharmacokinetic parameters
- CRRT procedure



Mortality in AKI (D)

PICARD Study



Overall mortality rate = 34%

Patients receiving IHD only mortality = 30%

Mortality for patients receiving CRRT in any form = 54%

Mortality for patients receiving CRRT only = 67%

CRRT Mortality in Major Trials

Trial

Mortality

Dose Trials (Standard vs High):

Tolwani 34 vs 59 90d

VA Cooperative 46 vs 56 60d

Renal 55% vs 55% 90d

Timing of CRRT Initiation Trials (Early vs Delayed):

IDEAL 48% vs 49.7%

AKIKI 58% vs 54%

Start AKI 43.9 vs 43.7

Time limited trials of RRT

- **Withholding and Withdrawing dialysis:** process requires joint decision making and ideally consensus between healthcare provider and patient/proxy.
- **A time-limited trial of RRT:** may be a good option in patients with ARF when prognosis is not clear or wishes for aggressive care are unknown
 - Initiated with the understanding that **dialysis will be withdrawn in a given period of time if clinical improvement does not occur.**
 - Goals of treatment, clinical outcomes to be assessed, and the **duration of the dialysis trial should be clear to all parties** and re-assessed as needed
 - During time-limited trials, **medical decision-making is an ongoing process** and allows for changes in the patient's clinical status and re-assessment of prognosis but within defined endpoints.

Conclusion

- Renal failure requiring RRT is a serious and costly complication of hospital admission
- Among the Nephrology community there is a strong sense of the importance of CRRT
- Mortality is high
- Decision making surrounding appropriate delivery of care is complicated.

Question 1

In Continuous Renal Replacement Therapies Filtration Fraction is the proportion of plasma water entering the dialyser that is removed by ultrafiltration. Higher filtration fractions ($>20\%$) are associated with increased filter clotting. A lower filtration fraction ($<20\%$) can be maintained by:

- A. Increasing ultrafiltration flow rate
- B. Increasing blood flow rate
- C. Using postfilter replacement fluid
- D. Using systemic citrate replacement fluid or regional citrate anticoagulation in preference to bicarbonate replacement fluid and heparin anticoagulation

Answer

B: Increasing blood flow rate.

In order to reduce the risk of increased filter clotting in the CRRT set up, recommendations include:

- Target a filtration fraction $< 20\%$
- Limit the ultrafiltration flow rate
- Increase blood flow rate (which determines plasma water flow rate)
- Use prefilter replacement fluid in CVVH or CVVHDF

Question 2

In patients on CRRT receiving either regional or systemic citrate anticoagulation the following abnormalities are associated with citrate accumulation (toxicity)

- A. Low serum calcium, low ionized calcium, metabolic alkalosis
- B. Low serum calcium, high ionized calcium, metabolic alkalosis
- C. High serum calcium, high ionized calcium, metabolic acidosis
- D. High serum calcium, low ionized calcium, metabolic acidosis

Answer

D. High serum calcium, low ionized calcium, metabolic acidosis

Citrate accumulation (toxicity) is due to the reduced conversion of the Calcium Citrate chelate to bicarbonate and ionized calcium which is performed primarily by the liver. The condition is most frequent in patients with disturbed liver function (shocked liver; chronic liver disease) where calcium citrate accumulation results in higher total calcium levels, low ionized calcium and metabolic acidosis (citrate is a weak acid).

Question 3

A 38 year old woman is admitted to ICU following an MVA with polytrauma including head injury with intracranial hemorrhage and rhabdomyolysis associated with crush injury. She is started on CVVH: Prismaflex 140Na; 0K; 2.5Ca; BFR 250cc/hr; Replacement fluid rate 1600 ml/hr. Neurosurgery is consulted and recommends Hypertonic saline infusion requesting a serum Na concentration of 150 meq/L.

A hypertonic 3% Saline drip is added. The infusion rate for the hypertonic saline should be:

- A. 30ml/hr
- B. 100/hr
- C. 44ml/hr

Answer

C. 44ml/hr

Hypertonic Saline Infusion in CRRT:

Estimated Infusion Rate =

$$(\text{Target Na} - \text{CRRT Na}) * (\text{QD} + \text{QRF}) / (513 - \text{Target Na})$$

$$= (150\text{mequi/L} - 140\text{mequi/L}) * (1600\text{ml/hr}) / (513\text{mequi/L} - 150\text{mequi/L})$$

$$= (10\text{mequi/L} * 1600\text{ml/hr}) / (363\text{mequi/L})$$

Estimated infusion Rate = 44 ml/hr