"When to start, how much to do and what does it mean?"
CRRT Initiation and Dosing

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- *University of Maryland Medical Center*

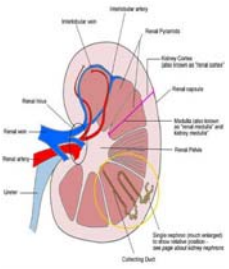
Objectives

1. Demonstrate understanding of AKI Physiology and the effect on homeostasis.
2. Identify a patient candidate for CRRT using the RIFLE/AKIN criteria as well as metabolic considerations for treatment initiation.
3. Demonstrate understanding of recent scientific evidence supporting optimum CRRT dose prescription.
4. Differentiate prescribed vs. delivered CRRT dose.
5. Identify a minimum of two elements that negatively effect CRRT dose delivery.

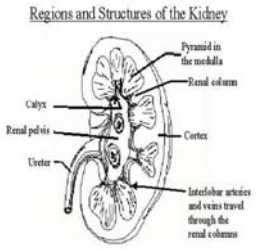
Normal Kidney Physiology

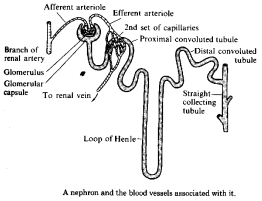
The Kidney

- Receives 20% of Cardiac Output!
- Regulates own blood flow.
  - Renin
  - Erythropoietin
  - Endothelium
- Cortex receives 80% with metabolically active region
- Medulla has anaerobic metabolism

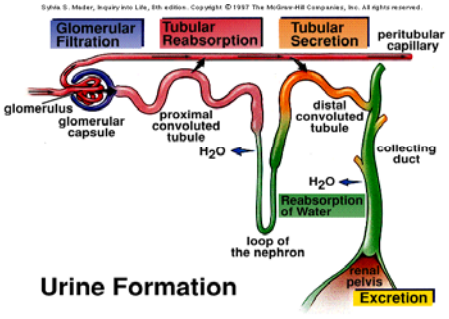


The Kidney and Nephron



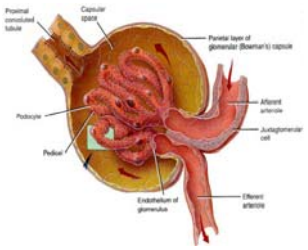


Urine Formation



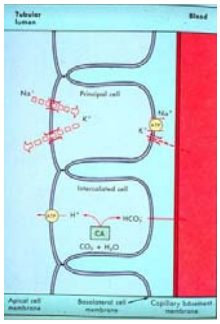
The Glomerulus

- Filtration takes place.
- Hydrostatic Pressure.
  - MAP (80-180 mm Hg)
  - Autoregulation fails below 70 mm Hg
- GFR = 125 mL/min
  - 180 L/day
  - 99% Reabsorbed



The Tubules

- Where the business takes place.
- Where the Sodium goes, so goes the water!
  - Na+/K+ Pumps
  - Requires ATP
- Proximal tubule reabsorbs 60-80% of filtrate through active reabsorbtion of NaCl



AKI Patient Physiology

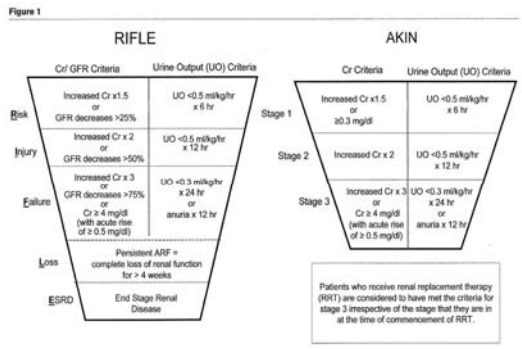
Typical Critically Ill AKI Patient Conditions

- **Hemodynamically Unstable**
- **Fluid Overloaded**
- **Renal Dysfunction (acute or chronic)**
- **Cardiac Dysfunction/Failure**
- **Sepsis**
- **MOF/MODS**
- **Rhabdomyolysis**
- **Liver Failure**
- **Burns**
- **ARDS**
- **Drug Overdose**
- **Post Cardiac Surgery**
- **Post organ transplant**

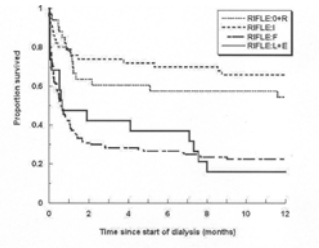
So what's the evidence?

AKI in the ICU

- Approximately 30,000 patients from 54 hospitals in 23 countries (including US)
- 6% of all ICU admissions developed AKI
  - Of these patients, approximately 70% required dialysis
- 30% of patients had renal impairment prior to development of AKI
  - 13% of patients were dialysis-dependent at discharge
- CRRT was initial dialysis modality in 80% of patients
- Hospital mortality of 60%



RIFLE Stratification in Patients Receiving CRRT



RENAL Trial Treatment Initiation Criteria

CRRT Initiation Criteria for AKI patients from the RENAL Study[1]

If the patient fulfilled ONE of the following clinical criteria, CRRT was initiated[1]

	Acute Kidney Injury (AKI) Clinical Markers			Other Critical Markers		
	Serum Creatinine	Urine Output	BUN	Serum Potassium	Volume Overload (with AKI)	pH
Normal Patient Values[2]	0.6 - 1.5 mg/dl	> 30 ml/hr	8 - 25 mg/dl	3.5 - 5 mEq/L		7.35 - 7.45
RENAL Initiation Criteria for CRRT[1]	>3.4 mg/dl	< 100 ml/6 hr*	> 70 mg/dl	> 6.5 mEq/L	Clinically significant organ edema	< 7.2

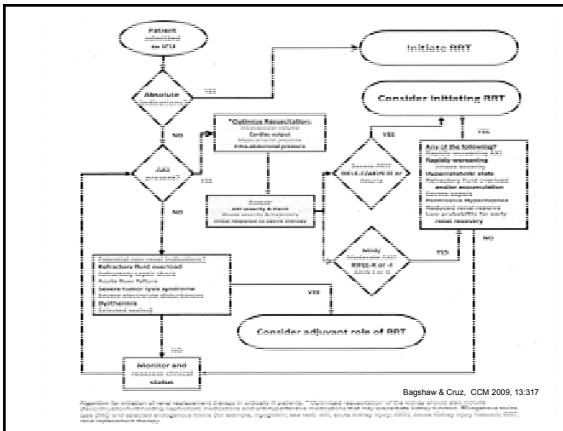
*unresponsive to fluid resuscitation measures

Other factors to consider…

Volume Overload: In a recent analysis of the Program to Improve Care in Acute Renal Disease (PICARD) database, fluid overload in AKI patients (defined as **>10%** fluid accumulation) was independently associated with mortality.[3]

Hemodynamic Stability: The ATN study used the CV SOFA score of 3-4 to determine which AKI patients were placed on CRRT or SLED** versus IHD.[4]

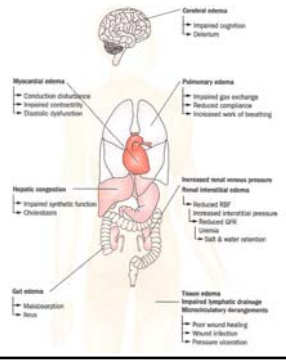
On average, CRRT was initiated 2.1 days from admission to the ICU in the RENAL Study.



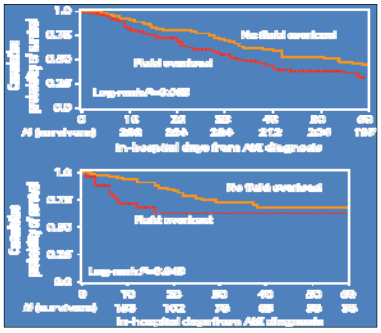
Bagshaw & Cruz. CCM 2009, 13:317

Should other non-renal indicators be considered?

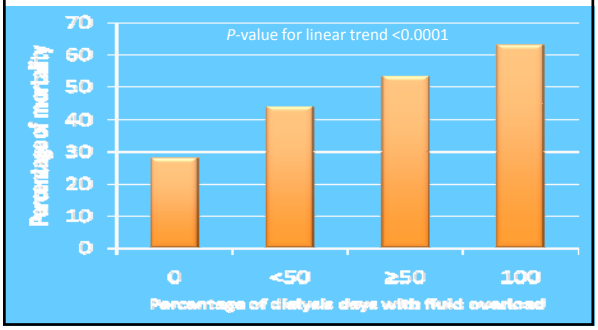
Potential Clinical Consequences of Organ Edema in Critically Ill Patients



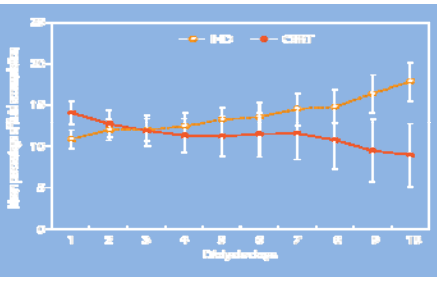
Effect of Fluid Overload on Survival in AKI
Bouchard et al, Kidney Int 2009



Effect of Duration of Fluid Overload on Mortality in Dialyzed AKI Patients
Bouchard et al, Kidney Int 2009



Correction of Fluid Overload: CRRT vs IHD
Bouchard et al, Kidney Int 2009



Effect of Diuretics on Outcome in AKI Patients

Table 2. Effect of Diuretics on Mortality and Nonrecovery of Renal Function Compared With No Diuretic Use*

Variable	OR (95% CI) Unadjusted	Covariate Adjusted	Covariate and Propensity Score Adjusted
In-hospital mortality	1.37 (0.97-1.92)	1.65 (1.05-2.58)	1.68 (1.06-2.64)
Nonrecovery of renal function	1.53 (1.08-2.15)	1.70 (1.14-2.53)†	1.79 (1.19-2.68)§
Death or nonrecovery	1.48 (1.02-2.12)	1.74 (1.12-2.68)‡	1.77 (1.14-2.76)‖

*Covariate adjusted for age; sex; log urine output; serum creatinine level; blood urea nitrogen level; respiratory, hepatic, and hematologic failure; and heart rate. The referent group was no diuretics; time was first day of intensive care unit consultation. OR indicates odds ratio; CI, confidence interval.
†Area under receiver operating characteristic (ROC) curve = 0.76; goodness-of-fit χ^2 P = .89.
‡Area under ROC curve = 0.82; goodness-of-fit χ^2 P = .39.
§Area under ROC curve = 0.85; goodness-of-fit χ^2 P = .84.
‖Area under ROC curve = 0.81; goodness-of-fit χ^2 P = .58.

Timing of RRT Initiation: Effect on Outcome

Bagshaw et al, J Crit Care 2008

Timing of Initiation	Crude Mortality (%)	OR for Death
Early (< 2 days)	58.9	1.0
Delayed (2-5 days)	62.1	1.19
Late (> 5 days)	72.8	2.20*

*: Significantly greater than Early group

Renal Replacement Therapy (RRT) Goals

- **Renal function replacement**
  - **Maintain fluid, electrolyte, acid/base balance**
  - **Eliminate waste product accumulation**

Renal recovery - Dialysis independence

- **Maintain hemodynamic stability (patient & treatment related)**
- **Prevent further damage to kidney tissue**

Renal support of homeostasis in all organ systems

- **Continuous RRT instead of intermittent RRT**
- **Neutral fluid balance**

How does RRT mimic normal kidney function?

Anatomy of a Hemofilter

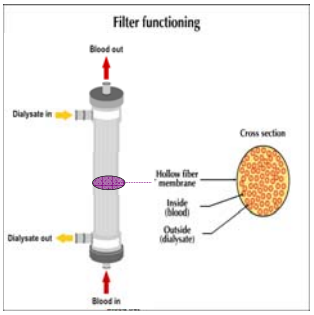
- Major Components:

✓ **4 External ports**
- Blood and dialysis fluid

✓ **Potting material**
- Seals both blood & fluid compartments

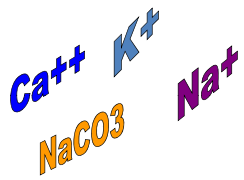
✓ **Hollow fibers**
- Semi-permeable membranes

✓ **Outer casing**



A major goal of RRT

- Electrolyte & pH Balance
  - Sodium
  - Potassium
  - Calcium
  - Glucose
  - Phosphate
  - Bicarbonate buffer



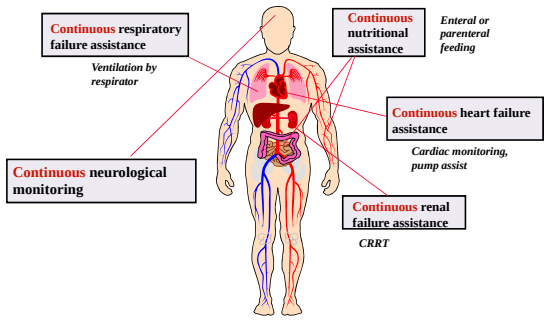
- Dialysate and replacement solutions are used in CRRT to attain this goal

AKI Modality Comparisons

- Three-step argument has been made
  - No substantial evidence that CRRT is superior even to conventional HD
  - SLED at least has to be equivalent to IHD
  - Therefore, SLED at least has to be equivalent to CRRT
- Can this argument be questioned in the age of "evidence-based medicine"?
  - Until a legitimate clinical trial comparing CRRT and SLED is performed, this view can be challenged

SLED Studies in "Mainstream" Literature

- Kumar, 2000 (US): **25 SLED patients** (HD machine)/**17 patients CVVH** patients (first-generation CRRT equipment) – no outcomes reported
- Lonnemann, 2000 (Germany): **20 SLED patients** (Genius)/**no CRRT** arm
- Marshall, 2001 (US): **37 SLED patients** (HD machine)/**no CRRT** arm
- Marshall, 2004 (NZ): **24 SLEDD-f patients** (FMC 4008 ArRT-Plus on-line HDF system)/**11 CRRT** patients – not an outcome study
- Kielstein, 2004 (Germany): **20 SLED patients** (Genius)/**19 CVVH** patients – not an outcome study
- Kumar, 2004 (US): **28 SLED** patients (HD machine)/**26 "CRRT"** patients (treated with conventional HD machine!) – not an outcome study
- Berbece and Richardson, 2006 (Canada): **23 SLED patients** (HD machine)/**11 CRRT** patients (non-concurrent) – not an outcome study
- Baldwin, 2008 (Australia): **8 SLEDD-f** patients/**8 CRRT** patients – not an outcome study
- Faulhaber-Walter, 2009 (Germany): negative dose study
- Wu et al, 2009 (Taiwan): **38 SLED** patients/**63 CRRT** patients (historical)
- Abe et al, 2010 (Japan): **only comparative RCT (N=60)**; negative study



Continuum of Care Treatment Goals

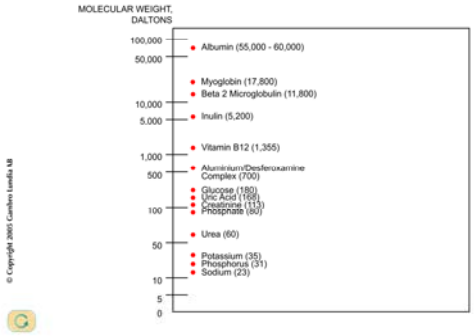
CRRT — IRRT

AKI Treatment Goals

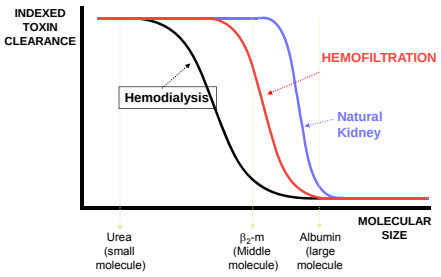
HUAKI
- Survival
- Renal Recovery
- Multi-organ support
- Net Neutral Fluid Balance

SAKI
- Survival
- Renal Recovery
- Net Neutral Fluid Balance

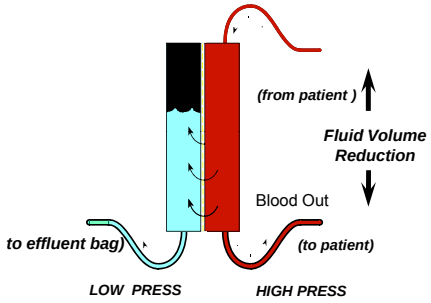
Molecular weights



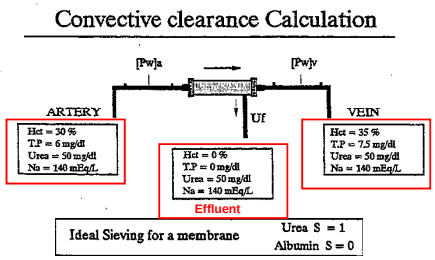
Clearance Profiles by Modality



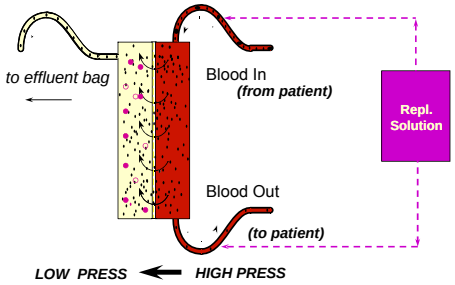
Ultrafiltration



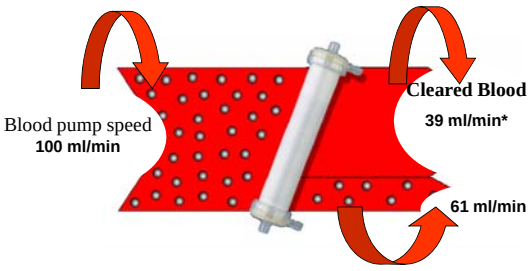
Convective Clearance Principle



Hemofiltration

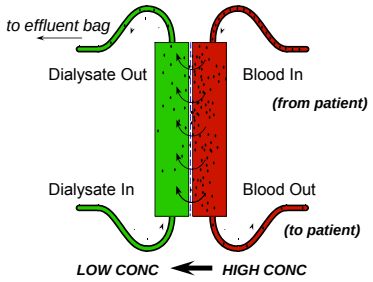


Diffusive Clearance Principle

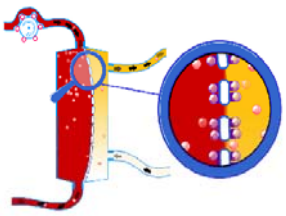


*Qd = 42 ml/min (2.5L/hr), UF = 0

Hemodialysis



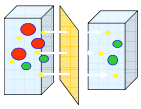
Adsorption



- Molecular adherence to the surface or interior of the membrane.

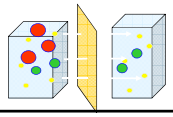
Diffusion vs. Convection

- Diffusion is solute transport across a semi-permeable membrane - molecules move from an area of higher to an area of lower concentration



Best for small molecule clearance

- Convection is a process where solutes pass across the semi-permeable membrane along with the solvent ("solvent drag") in response to a positive transmembrane pressure



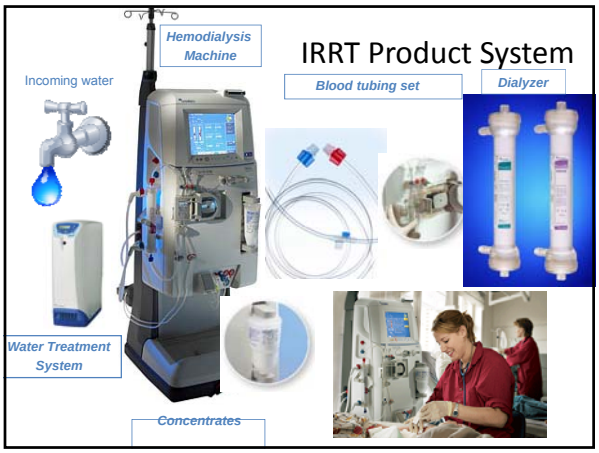
Effectiveness less dependent on molecular size

CRRT vs. IRRT

- Continuous RRT
- Duration = 24 hours
- Blood Flow = 150 to 250 ml/min
- Fluids used = Dialysate & Replacement
- Fluid Rates = 34 to 68 ml/min
- Sterile Dialysate and Replacement
- Typical Net Fluid Removal = 0 - 100 ml/hr
- Molecular movement = small, medium, large (up to 50,000 Daltons)

- Intermittent RRT
- Duration = 3 to 4 hours
- Blood Flow = 300 to 400 ml/min
- Fluids used = Dialysate only
- Fluid Rates = 500 to 800 ml/min
- Non Sterile Dialysate
- Typical Net Fluid Removal = 0-1000 ml/hr
- Molecular movement = small, medium

CRRT Product System



Different Approaches for SLED/EDD

Table 1 | Treatment parameters for current and previous SLED studies

Author (reference)	Kumar *et al.*[4]	Marshall *et al.*[5]	Marshall *et al.*[6]	This study
Treatment name	EDD	SLED	SLEDD-*f*	SLED
Hours/day	7.5	12	8	8
Days/week	6–7	6–7	4–7	6
Blood pump speed (ml/min)	200	100	300	200
Dialysate flow (ml/min)	300	200	200	350
Replacement fluid (ml/min)	—	—	100	17

EDD, extended daily dialysis; SLED, sustained low-efficiency dialysis; SLEDD-*f*, sustained low-efficiency daily diafiltration.

Small Solute Removal: SLED vs CRRT

Table 4 | Measures of small solute removal

	CRRT	SLED	*P*-value
Morning serum creatinine after day 3 (μmol/l)	136±49	120±55	0.06
Time-averaged serum creatinine (μmol/l)	136±49	95±49	0.03
Weekly K_r/V	7.1±2.1	8.4±1.8	<0.001
EKR_J (ml/min)	31±10	31±7	NS
EKR_{Ic} (ml/min)	28±9	29±6	NS

CRRT, continuous renal replacement therapy; NS, not significant; SLED, sustained low-efficiency dialysis.

Solute Mass Removal: CVVH vs EDD

	CVVH	Extended Dialysis
Total urea removed (g)	73.1 ± 7.7	71.8 ± 7.2
Total creatinine removed (g)	1.20 ± 0.13	1.18 ± 0.09
Total β_2-microglobulin removed (g)	0.29 ± 0.03	0.15 ± 0.02*

NOTE. Solutes removed were measured in samples obtained from collected spent total dialysate and hemofiltration fluid in all treated patients.

*$P < 0.01$, comparison between CVVH and extended dialysis.

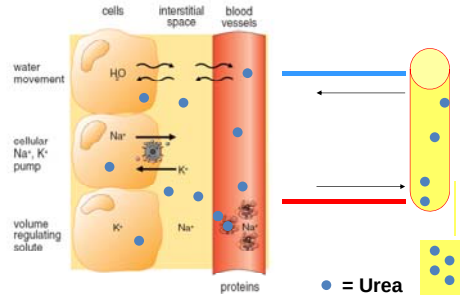
HANDOUT Study: Intensified vs Standard EDD Faulhaber-Walter et al, Nephrol Dial Transplant 2009

We cannot rule out that the lack of benefit of a higher dialysis dose is due to the fact that we solely studied a mainly diffusive mode of RRT. Indeed, ED has been shown to be inferior in removal of beta-2 microglobulin [12] indicating an inferior clearance of middle molecules. The same could hold true for mediators and cytokines, which, however, had not been studied in our population. Hence, it is possible that a higher removal of mediators and cytokines from the blood compartment in the proinflammatory phase of sepsis using convective modes of RRT might provide a benefit for selected patients.

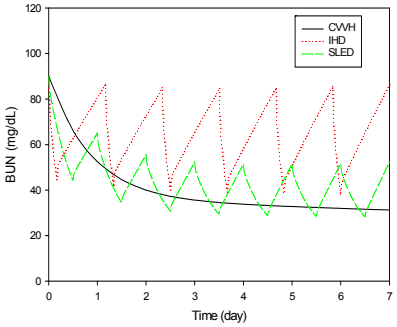
CRRT vs SLED: Outcome Data

- SLED/EDD has now been used for more than a decade
  - Lack of ***meaningful*** outcome data raises major questions
- Absent or incomplete clinical information for SLED
  - Basic prescription information: frequency; duration; type of filter
  - Dialysate/fluid requirements
  - Effect of SLED dose on survival
  - Effect of SLED on recovery of renal function
- This missing information for SLED contrasts with the available medical evidence for CRRT

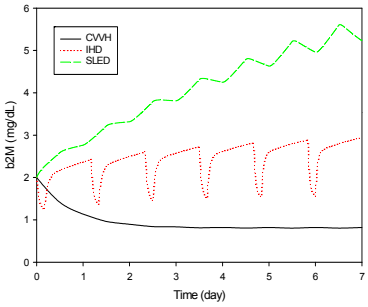
Waste Product Removal = CRRT Dose



Azotemia Control Profiles
Liao et al., Artif Organs



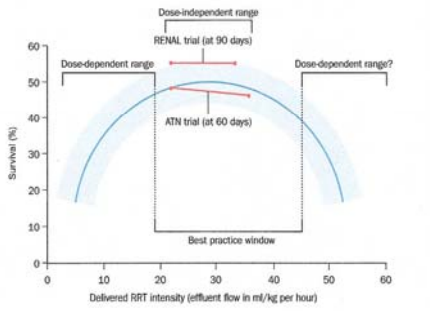
2 Microglobulin Concentration Profiles
Liao et al., Artif Organs 2003



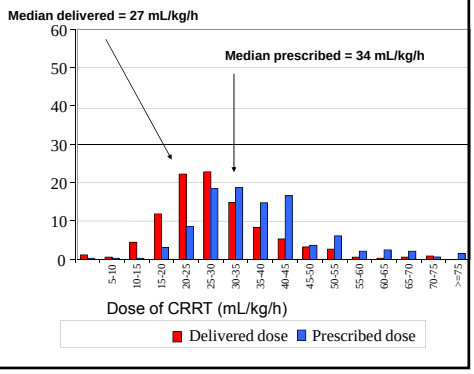
Comparisons of Major CRRT Dose Trials

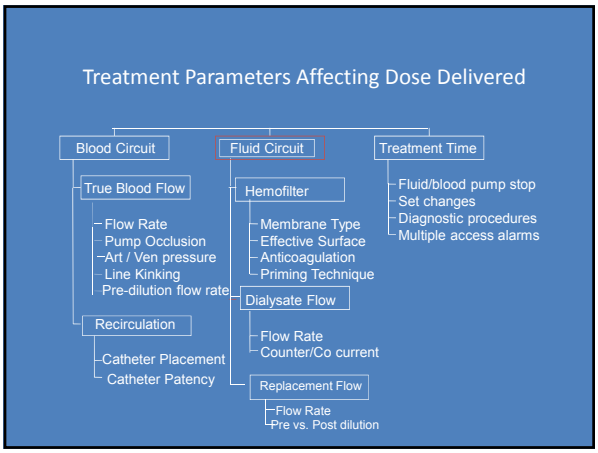
	Ronco	Saudan	Tolwani	ATN	RENAL
# Patients	425	206	200	1124	1508
RCT (M-C)	No	No	No	Yes	Yes
CKD (%)	NA	33	42	Excluded	Included
Major AKI Cause	Surgical	Sepsis	Sepsis	Ischemia	Ischemia
APACHE II	~23	25	26	~29	~26
Init BUN (mg/dl)	53	83	75	65	65
Modality	post CVVH	pre CVVHDF	pre CVVHDF	pre CVVHDF	post CVVHDF
% Convective	100	~60	43-44	50	50
Rx Dose (ml/kg/hr)	20/35/45	25/42	20/35	20/35	25/40
Del Dose (ml/kg/hr)	20/35/45	~ 20/37	~17/29	~17/27	22/34
ICU Wait (days)	NA	NA	11	6.9	2.1
Survival	57% (p=0.001)	59% (p=0.03)	49% (p=0.32)	46.4% (p=0.47)	45% (p=0.99)

Delivered CRRT Dose: Best Practice Window
Kellum and Ronco, Nature Reviews Nephrol 2010



DoReMi Database (N=865)





CRRT Dose Summary

- CRRT dose = elimination of waste products (urea) which is a traditional marker of dialysis efficacy in chronic patients
- Critically ill AKI patients are very different from chronic kidney patients and newer biomarkers of efficacy are currently being explored
- Urea is present in all body fluids (intra & extracellular)
- CRRT dose delivery is affected by many patient and treatment variables
- CRRT dose is typically under-delivered and this may impact patient outcomes

Major take-aways

- Normal renal function is required to maintain homeostasis, including fluid balance, renal dysfunction/injury negatively impacts homeostasis!
- RIFLE/AKIN criteria is used to identify the stages of kidney dysfunction & to predict associated mortality!
- Fluid overload is independently associated with mortality & is sometimes used as a marker for treatment initiation!

Major take-aways

- RENAL Trial treatment initiation criteria when used with Drs. Bagshaw and Cruz's algorithm can provide practical bedside information!
- Diuretics need further study, but may negatively impact survival and renal recovery!
- While further study is needed, earlier CRRT initiation may result in improved outcomes compared to late CRRT initiation!

Major take-aways

- Ensure your CRRT dose prescription is delivered!
- The Do-Re-Mi study suggests prescribing 30 ml/kg/hr in order to ensure delivery of 25ml/kg/hr
- Urea is a traditional marker for chronic dialysis efficacy, CRRT provides benefits above and beyond urea clearance

Major take-aways

- Major contributors to under-delivery of CRRT dose can be patient or treatment related
- CRRT provides slow, continuous and gentle replacement of renal function…as close to native kidney function as possible!