RENAL SUPPORT IN THE HEMODYNAMICALLY UNSTABLE PATIENT: CONTINUOUS OR PROLONGED INTERMITTENT?

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AKI 2010
Acute Kidney Injury and Renal Support

Edmonton April 16, 2010

Renal Support: What's needed?

Strategies for Management of Renal Failure

	AKI	ESRD
Goals of therapy	Improve OSF	Ameliorate uremia
Desired Outcome	Survival Recovery of renal function	Long term survival Quality of Life
Determining Factor	Other Organ Function	Renal Process
Indication for dialysis	Renal Support	Renal Replacement

Mehta: Blood Purif. 2001;19(2):227-32.

The changing paradigm of dialysis in the ICU

	Renal Replacement	Renal Support
Purpose	Replace renal function	Support other organs
Timing of Intervention	Based on level of biochemical markers	Based on individualized need
Indications for Dialysis	Narrow	Broad
Dialysis Dose	Extrapolated from ESRD	Targeted for overall support
Application	Renal Failure	Renal and Non-renal indications

RL Mehta: Indications for dialysis in the ICU: renal replacement vs. renal support. Blood Purif. 2001;19(2):227-32.

Potential Indications for Dialysis in Critically Ill

Renal Replacement		**Renal Support**
Life Threatening Indications	Hyperkalemia Acidemia Pulmonary edema Uremic complications	Nutrition Fluid removal in congestive heart failure Cytokine manipulation in sepsis Cancer chemotherapy Treatment of respiratory acidosis in ARDS Fluid management in multi-organ failure
Solute control Fluid removal Regulation of acid-base and electrolyte status		

RL Mehta: Indications for dialysis in the ICU: renal replacement vs. renal support. Blood Purif. 2001;19(2):227-32.

Renal Support: What's needed?

- Renal Support should be comprehensive

Therapeutic Targets for RRT

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

Operational Characteristics of RRT Applicable for Renal Support

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

Renal Replacement Therapy in AKI

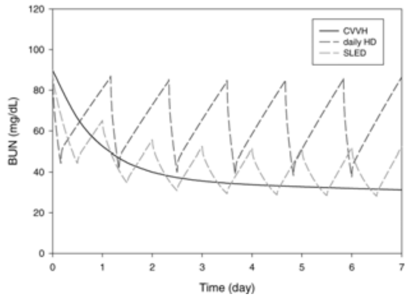
(Adapted from Schlaeper *et al.*, Kidney Int 1999)

	IHD	SLED/EDD	CVVHD	CVVH
Blood Flow Rate (mL/min)	200-300	100-300	150-200	150-300
Dialysate Flow Rate (mL/min)	500-800	100	20-40	—
Ultrafiltration Rate (mL/min)	variable	variable	variable	20-40
% Saturation	15-40	60-70	85-100	100
Daily Kt/V*	1.2	1.2	1.2	1.2
EKRurea (mL/min)#	variable	~25	20-40	20-40

*Assumes V = 36 L

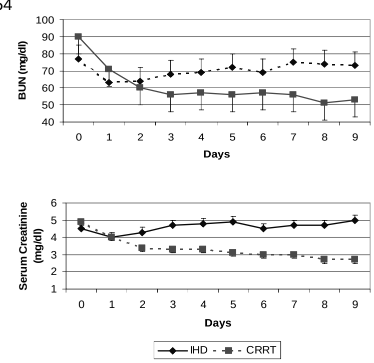
$EKR = \frac{G}{C}$

Azotemia control profiles in CVVH, daily HD, and SLED



Liao, Z et al Kinetic Comparison of Different Acute Dialysis Therapies. *Artificial Organs* 2003, **27** (9), 802-807

Mehta et al: A Randomized Clinical Trial of Continuous vs. Intermittent Dialysis for Acute Renal Failure. Kidney Int 2001; 60:1154



Comparisons of Fluid Management Capability

	Normal Kidney	*Intermittent HD**	*Peritoneal Dialysis*	*CRRT#*
Ultrafiltration (ml/min)	*120*	*34*	*14*	*100*
Volume of Filtrate /day (L)	*173*	*8*	*14*	*144*
Volume removed /Day (L)	*0.1-1.5*	*0-8*	*0-14*	*0-100*
Regulatory mechanism	*GFR Control*	*UFR Control*	*UFR control*	*UFR Control*
	Reabsorption	-	-	*Replacement Fluid*
Sensing mechanism	*Hemodynamic*	-	-	*-? hemodynamic*
	Volume status	-	-	*? volume status*

** 4 hours /day*

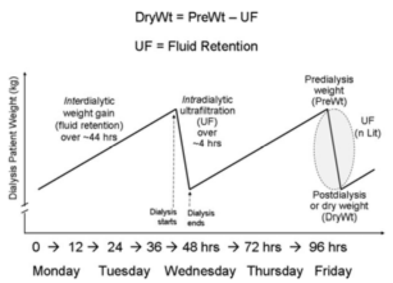
 # High volume HF 6L/hr

Fluid removal vs Fluid regulation

	Fluid removal	Fluid regulation
Normal Kidney	+++	++++
Intermittent Hemodialysis	+++	-
Peritoneal Dialysis	++	-
CRRT	+++	+++

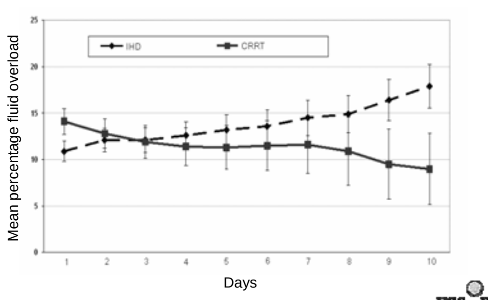
Changes in Fluid Balance in Intermittent Dialysis

Schematic representation of the bidiurnal variation of fluid status in chronic hemodialysis patients. Between the 2 subsequent dialysis treatment sessions, usually 44 hours apart, the patient's interdialytic weight gain reflects fluid retention between 2 consecutive hemodialysis treatments, which will then be removed rather quickly via dialysis ultrafiltration (UF) during a 4-hour dialysis treatment. DryWt indicates dry weight; PreWt, predialysis weight; and n Lit, magnitude of ultrafiltered fluid in liter.

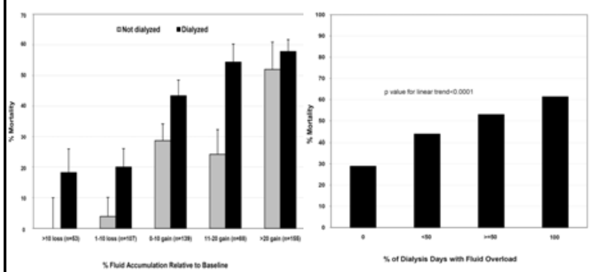


Kalantar-Zadeh et al: ***Circulation. 2009;119:671-679.***

Influence of Modality on Fluid Overload



Influence of Fluid Accumulation on Mortality



- **Adjusted OR for death with % FO >10% at dialysis initiation:**

  2.07 (95% CI 1.27-3.37)

Kidney Int. 2009 May 13. [Epub ahead of print]

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Operational Characteristics of RRT Applicable for Renal Support

Parameters	CRRT attributes
Solute clearance: Electrolytes; Acid Base Balance; Amino acid removal	Solute concentration can be manipulated independent of fluid balance
Fluid regulation: Space; Pressor support	Plasma composition can be altered by changing composition of dialysate and substitution fluid
Modulation of Mediators: Removal of hepatotoxic factors; Adsorption	Fluid regulation can occur concurrently with solute removal to maintain patient fluid balance desired
Thermal Control: Hemodynamic support; Cerebral Edema	Core temperature regulation can be achieved

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Renal Support: What's needed?

- Renal Support should be comprehensive
- Renal support needs to match patient need

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Patient Need

- Patients span spectrum of severity at initial evaluation
- Change in severity of illness is common during the course and predicts outcomes
- Therapeutic Modalities need to support organ function

Case Study

- **21-year-old young woman underwent a normal term uneventful delivery 3 days ago (7/05).**
- **Post-partum noted to have a progressive decrease in her platelet count, and an increase in her creatinine.**
- **No past medical history, has been healthy**
- **Second pregnancy, first one resulted in a miscarriage**
- **Variable pre-partum follow-up, normal BP and only trace proteinuria, platelet counts about 200,000.**
- **On admission, the platelet count was 172,000 progressively decreased to 27,000 on day of consultation.**
- **She does not smoke, use alcohol, or any drugs. She has had no prior hospitalization.**
- **ROS: Unremarkable. No change in urine output**

Case Study (cont'd.)

- **PHYSICAL EXAMINATION:**
  - Afebrile, BP 130/70, HR 70, **CVS:** Normal heart sounds **LUNGS:** Clear with good air entry bilaterally, **ABDOMEN:** Soft, postpartum, nontender. **CNS:** Normal, **EXTREMITIES:** no edema.
- **LABs (consult day)**
  - **:** Na 136, K 4.1, Cl 126, Bicarb 22, **BUN 30** and **creatinine 1.5** mg/dl, glucose 125, Ca 8.5, T prot 4.3 with an **albumin of 1.7**, AST 86, ALT 39, **LDH 2122** with **total bilirubin of 1.6** and direct of 0.4. Alkaline phosphatase 24. **Creatinine on 07/07 had been 0.8**, 1 07/08 AM, 1.2 07/08 PM, and 1.5 07/09.
  - WBC13,000, Hb 6, Hct 18.6. **Platelets are 27,000.** Her peripheral smear shows schistocytes. Her platelet count has decreased from 170,000 on 07/05 to 75 on 07/07, and now 27,000.
  - UA: **1+ protein**, 3-5 RBC, > 50 RBC's and occ hyaline cast

Case Study : Differential Diagnosis at Initial Presentation

TTP/HUS

Acute Fatty Liver of Pregnancy (AFLP)

HELLP

DIC

PreEclampsia

Abnormality	HUS/TTP	AFLP	HELLP	DIC	Preeclampsia
Abnormal PT/PTT	N	Y	N	Y	Y or N
Hemolysis	Y	Y	Y	Y	Y
Thrombocytopenia	Y	Y	Y	Y	Y
Abnormal liver function tests	N	Y	Y	N	N
Abnormal renal function tests	Y	N	N	N	N

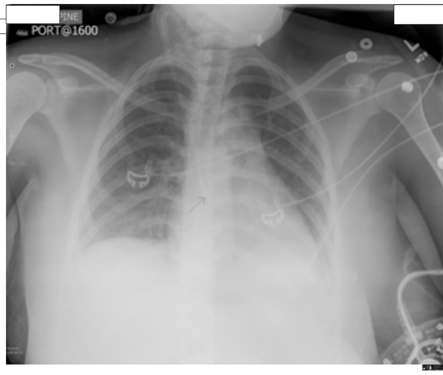
Case Study (cont'd.)

- **Course**
  - **Started on plasmapheresis for presumed diagnosis of post-partum HUS/TTP**
  - **IJ Vascath, Centrifugal, citrate protocol 3.5L exchange with 3.5L FFP**
  - **During the plasma exchange procedure received 1unit packed RBC's**
  - **Within 60 minutes of procedure, became progressively short of breath, had increasing oxygen requirements and was transferred to ICU with 95% face mask.**

Case Study (cont'd.)

- **PHYSICAL EXAMINATION:** HR 70, BP 140/80. normal heart sounds. **Lungs** show diffuse crackles bilaterally, all the way up to the upper lung fields. Abdomen is soft. Extremities show no edema.
- **Urine Output** 50 to 75 mL per hour.
- **LABs:** Sodium 142, potassium 3.6, chloride 104, bicarbonate 28, **BUN and creatinine of 28 and 1.8,** glucose 117. Calcium is 8.3. Phosphate is 6 and magnesium 3. **Albumin is 2.4.** LFTs show an **SGOT of 81 and SGPT of 41.** Total bilirubin was 3. **LDH was 1410, down from 2122 yesterday. WBC 11.3, hemoglobin 6.9, and hematocrit 19.6, with platelets of 25,000.**
- **CHEST X-RAY:** Shows diffuse infiltrates over both her lung fields which is significantly different from the one prior to the procedure

Case Study (cont'd.)



Case Study: Differential Diagnosis Post Pheresis

- Acute pulmonary edema
- Pulmonary embolism
- Anaphylaxis
- Septic Shock from bacterial contamination
- TRALI

Case Study (cont'd.)

Case Study (cont'd.)

- **DAY 2 of CONSULT:** A second plasma exchange treatment was started.
- Initially uneventful, but towards the end, when she was getting a transfusion started, worsening respiratory status, shortness of breath, and required intubation.
- Marked bleeding from the upper airways, bronchoscopy showed alveolar hemorrhage. Initially on 100% FiO_2, subsequently weaned to 60%.
- **On Exam**
  - Intubated/sedated, with an FiO_2 of 60%. HR 100, BP 120/80, Normal heart sounds. Lungs show diffuse crackles all the way up the upper lung fields. Abdomen is soft. Extremities no edema.
  - Urine output about 5-10 mL/hr.

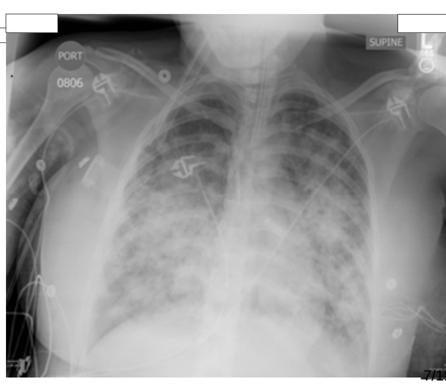
Case Study (cont'd.)

LABORATORY: Sodium of 145, potassium 3.3, chloride 101, bicarb 31, and **BUN 51** and **creatinine 2.3 mg/dl**. Calcium is 8.2, phosphate 6.7, magnesium 2.3, albumin 2.9. LDH is 1536, up from 1069 post-pheresis. **WBC is 21.1** and **hemoglobin 7.4**. She was transfused 1 more unit. Her platelets are 88,000 relating the platelet transfusion also given after the intubation event. Her fibrinogen is 321. ABG is pH 7.4, pCO_2 43, and pO_2 105.

CHEST X-RAY: Shows increased B/L infiltrates

QUESTION: What is the differential diagnosis, and what should be done next?

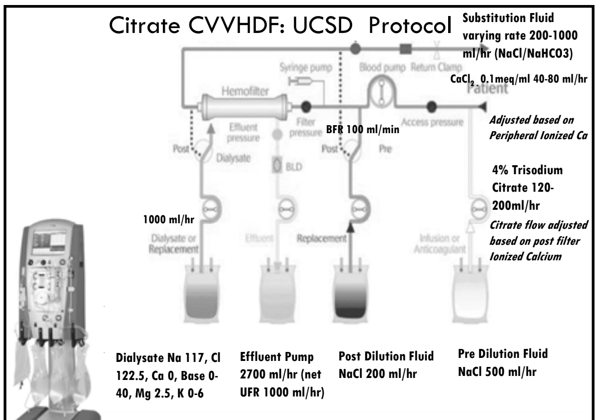
Case Study (cont'd.)



Case Study

- Course
- Started on CVVHDF

Citrate CVVHDF: UCSD Protocol



Hydraulic Circuit for PrismaFlex

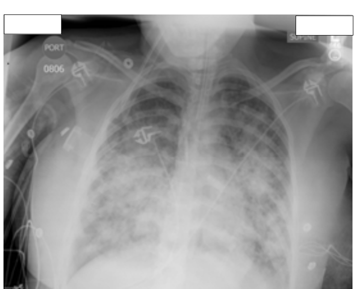
Case Study (Course 7/12 cont'd.)

Maintained on CRRT with citrate anticoagulation

Effluent vol 2.7L/hr and fluid balance -100 ml/hr and gradually increased to -125ml/hr

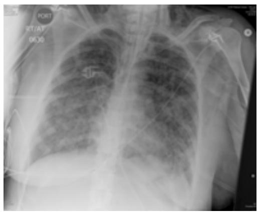
Plasma exchange continued for TTP

Improved oxygenation

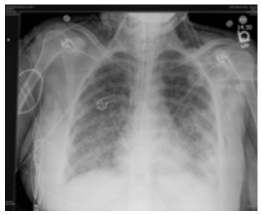


Case Study (cont'd.)

7/12 7AM

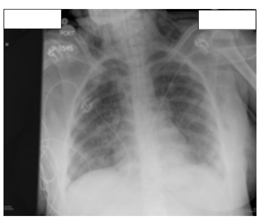


7/12 2:30PM

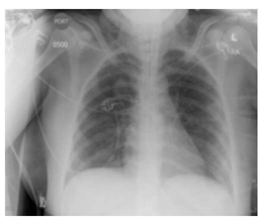


Case Study (cont'd.)

7/13 5 AM



7/14 6:15AM



Case Study (Course cont'd.)

Maintained on CRRT with citrate anticoagulation

- Plasma Exchange 12 units FFP continued for 4 weeks and then tapered
- Required tracheostomy at day 7
- Patient switched to IHD after 10 days
- Recovered renal function and was discharged from hospital at 5 weeks

Renal Support: What's needed?

- Renal Support should be comprehensive
- Renal support needs to match patient need
- Renal Support should improve outcomes

Does RRT Provide Any Outcome Benefit?

- Which Outcomes?
  - Mortality (time point)
  - Renal Recovery (definition)
  - Dialysis Dependence
  - Complications
  - Economic
- Evidence
  - Observational studies
  - Randomized Trials
  - Metanalysis

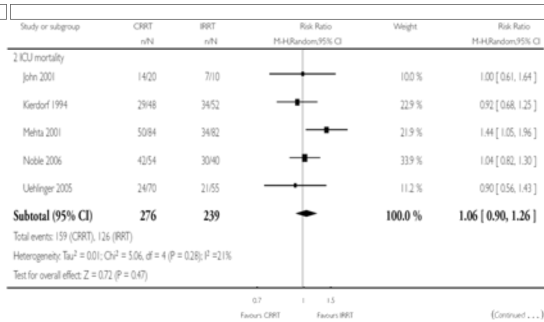
Uchino et al: Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury The International Journal of Artificial Organs / Vol. 30 / 2007 / pp. 281-292

TABLE IV - OUTCOMES OF PATIENTS TREATED WITH RENAL REPLACEMENT THERAPY

	Total	CRRT	IRRT	
Duration of RRT (days)	6 (3 - 15)	6 (3 - 15)	7 (3 - 19)	p=0.26
Patients discharged without RRT	6 (3 - 16)	6 (3 - 16)	7 (2 - 20)	p=0.095
Patients who died	6 (3 - 15)	6 (3 - 14)	8 (3 - 18)	p=0.76
Length of ICU stay (days)	12 (5 - 24)	12 (5 - 23)	12 (6 - 25)	p=0.70
Patients who survived	13 (7 - 26)	14 (8 - 26)	11 (5 - 25)	p=0.023
Patients who died	11 (4 - 23)	11 (4 - 22)	14 (7 - 25)	p=0.040
Length of hospital stay (days)	25 (12 - 48)	24 (12 - 47)	28 (14 - 50)	p=0.14
Patients who survived	37 (20 - 63)	38 (21 - 70)	35 (19 - 55)	p=0.22
Patients who died	18 (9 - 37)	18 (9 - 36)	20 (9 - 43)	p=0.14
Hospital survival	38.6%	35.8%	51.9%	p<0.0001
Dialysis-free hospital survival	31.3%	30.6%	34.3%	p=0.33
Off dialysis at hospital discharge	92.7%	94.8%	82.5%	p<0.0001
Among survivors	80.9%	85.5%	66.1%	p<0.0001
Creatinine (μmol/L) *	114 (84 - 176)	109 (82 - 170)	133 (88 - 202)	p=0.041
Urea (mmol/L) *	9.5 (6.5 - 15.5)	9.4 (6.5 - 15.0)	10.2 (6.5 - 17.8)	p=0.41

RRT: renal replacement therapy, *: for patients who were discharged from hospital without RRT.

CRRT vs IRRT: effect on Mortality: ICU
Cochrane Database Review 2007



RabindraNath KJ et al: Cochrane Database Syst Rev. 2007 Jul 18;(3):CD003773.

Uchino et al: Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury The International Journal of Artificial Organs / Vol. 30 / 2007 / pp. 281-292

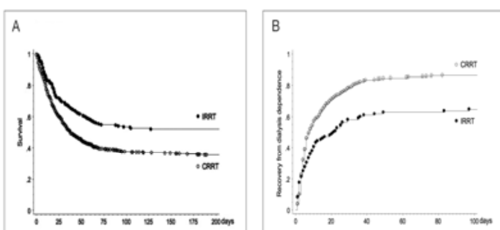


Fig. 1 - ***(a)*** *Kaplan-Meier product limit plot for survival. White circles represent patients treated with CRRT; black circles represent patients treated with IRRT. CRRT = continuous renal replacement therapy; IRRT = intermittent renal replacement therapy.* ***(b)*** *Inverted Kaplan-Meier product limit plot for dialysis dependence among survivors of acute renal failure. White circles represent patients treated with CRRT and black circles represent patients treated with IRRT. CRRT = continuous renal replacement therapy. IRRT = intermittent renal replacement therapy.*

Uchino et al: Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury The International Journal of Artificial Organs / Vol. 30 / 2007 / pp. 281-292

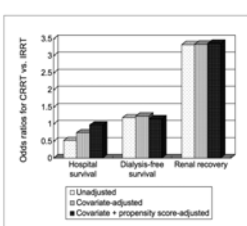


Fig. 2 - *Odds ratios for CRRT compared to IRRT for hospital survival, dialysis-free survival and renal recovery. Shown are the unadjusted, covariate-adjusted and covariate + propensity score-adjusted Odds Ratios for CRRT, using IRRT as the reference.*

TABLE VII - MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS FOR HOSPITAL SURVIVAL WITH PROPENSITY SCORE

	Odds ratio (95% CI)	
Age (years)	0.975 (0.966 - 0.985)	p<0.0001
From hospital to ICU (days)	0.951 (0.932 - 0.97)	p<0.0001
Platelet count (*10³/μL)	1.003 (1.002 - 1.004)	p<0.0001
Creatinine (μmol/L)	1.003 (1.002 - 1.004)	p<0.0001
pH	30.92 (6.675 - 143.0)	p<0.0001
CF: sepsis / septic shock	0.534 (0.390 - 0.731)	p<0.0001
Mechanical ventilation	0.461 (0.304 - 0.699)	p=0.0003
CF: Hepato-renal syndrome	0.330 (0.173 - 0.629)	p=0.0008
SAPS-II (points)	0.986 (0.977 - 0.994)	p=0.0013
MAP (mmHg)	1.014 (1.004 - 1.025)	p=0.0074
CF: low cardiac output	0.623 (0.440 - 0.882)	p=0.0077
Reason: High urea / creatinine	0.652 (0.473 - 0.900)	p=0.0092
Vasopressors / inotropes	0.635 (0.441 - 0.916)	p=0.015
Other diuretics	0.495 (0.278 - 0.882)	p=0.017
Furosemide (mg/6hrs)	0.998 (0.997 - 1.000)	p=0.018
Urine output (ml/6hrs)	1.001 (1.000 - 1.001)	p=0.032
Propensity score	1.721 (1.345 - 2.202)	p=0.0001
CRRT	0.970 (0.644 - 1.461)	p=0.88

Comparison of Dialysis Modalities in Critically Ill Patients

- No evidence for superiority of any technique for outcomes of mortality,
- CRRT techniques may have better chance for renal recovery
- Complications varied
  - More hemodynamic stability with CRRT
  - Higher clotting rates in non-citrate CRRT
  - No difference in bleeding risks

Renal Support: What's needed?

- Renal Support should be comprehensive
- Renal support needs to match patient need
- Renal Support should improve outcomes
- Renal Support needs to be broad based

Renal Support in the Hemodynamically Unstable Patient

- CRRT is the Unmatched Choice and even my opponent says so!

Uchino et al Acute Renal Failure in Critically Ill Patients: A Multinational, Multicenter Study.

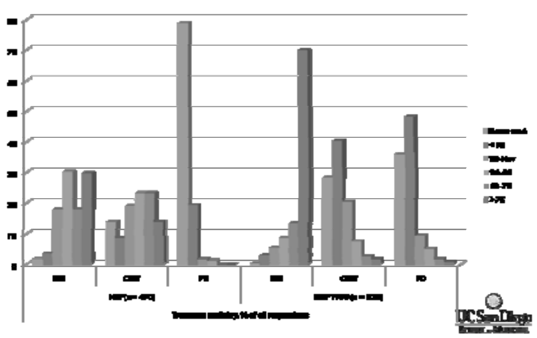
Age (years)	66 (51–74)
Gender (male)	662/1006 (65.8%)
Premorbid renal function	
Normal	590/1006 (58.6%)
Chronic impairment	283/1006 (28.1%)
Unknown	133/1006 (13.2%)
SAPS II	48 (39–62)
Predicted mortality (%)	41.5 (23.0–71.4)
Hospital to ICU (days)	1 (0–7)
ICU to start (days)	1.2 (0.4–4.1)
Contributing factors to ARF	
Sepsis/septic shock	504/1003 (50.2%)
Major surgery	377/1003 (37.6%)
Low cardiac output	262/1003 (26.1%)
Hypovolemia	201/1003 (20.0%)
Drug induced	176/1003 (17.5%)
Hepatorenal syndrome	73/1003 (7.3%)
Obstructive uropathy	20/1003 (2.0%)
Others	114/1003 (11.4%)
Reasons to start CRRT	
Oliguria/anuria	703/1002 (70.2%)
High urea/creatinine	531/1002 (53.0%)
Metabolic acidosis	437/1002 (43.6%)
Fluid overload	368/1002 (36.7%)
Hyperkalemia	186/1002 (18.6%)
Immunomodulation	136/1002 (13.6%)
Others	70/1002 (7.0%)
ICU mortality	555/1003 (55.3%)
Hospital mortality	641/ 999 (64.2%)
SMR	1.38 (1.28–1.50)

CRRT mode	
CVVH	531/1006 (52.8%)
CVVHDF	342/1006 (34.0%)
CVVHD	132/1006 (13.1%)
CAVHD	1/1006 (0.1%)
Dilution site for replacement fluid	
Predilution	509/870 (58.5%)
Postdilution	361/870 (41.5%)
Filter material	
Polyacrylonitrile	457/975 (46.9%)
Polysulfone	209/975 (21.4%)
Polyamide	164/975 (16.8%)
Cellulose triacetate	89/975 (9.1%)
Polymethyl-methacrylate	27/975 (2.8%)
Polyarylether-sulfone	14/975 (1.4%)
Cellulose diacetate	11/975 (1.1%)
Others [a]	4/975 (0.4%)
Anticoagulation	
Unfractionated heparin	429/1000 (42.9%)
Sodium citrate	99/1000 (9.9%)
Nafamostat mesilate	61/1000 (6.1%)
Low-molecular-weight heparin	44/1000 (4.4%)
Prostacyclin	11/1000 (1.1%)
Hirudin	9/1000 (0.9%)
Heparin-protamine	6/1000 (0.6%)
Others [b]	3/1000 (0.3%)
Combination [c]	7/1000 (0.7%)
No anticoagulation	331/1000 (33.1%)

Intensive Care Med (2007) 33:1563–1570

Utilization of renal replacement therapy for critically ill patients 2008

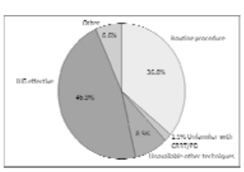
Fred Lai, and Ravindra L. Mehta, UCSD , San Diego

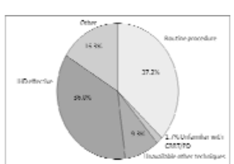


Reasons for Using IHD instead of CRRT or PD

NKF (n = 490)

SCCM (n=253)

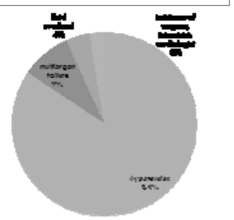


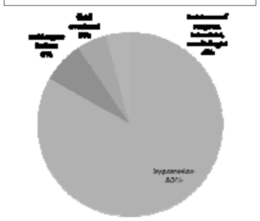


Lai and Mehta US Survey 2008

Reasons for Using CRRT instead of IHD or PD

NKF (n = 490)	SCCM (n=253)

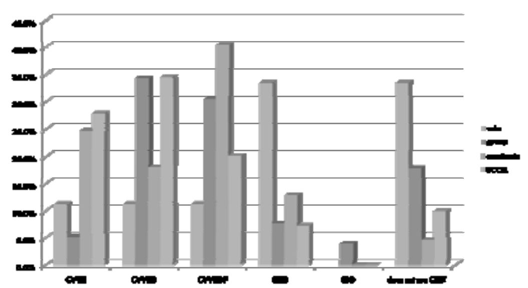




Lai and Mehta US Survey 2008

Utilization of renal replacement therapy for critically ill patients 2008

Fred Lai, and Ravindra L. Mehta, UCSD , San Diego



Transitions in Therapy in RRT for AKI

Study	Transition to CRRT	Transition to IHD
Mehta 2002	15/82	17/84
Augustine 2004	6/40	9/40
Mehta (PICARD)	24%	40%
Uchino 2005	9%	18.2%
Vinsonneau 2007	6/23*	17/23*
Palevsky 2008**	?	?

*Transitions not part of protocol.

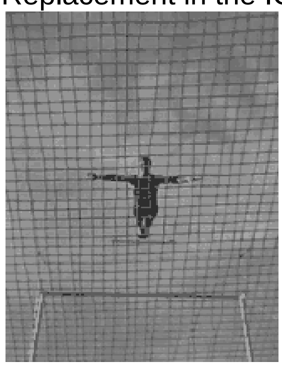
**23% only CRRT, 20% only IHD; 57% had more than one modality and often more than one transition

Renal Support for the hemodynamically unstable patient : CRRT is it!

- CRRT can be used for comprehensive continuous organ support in ICU patients
- Flexibility and adaptability of this technique facilitates its use for a wide variety of indications
- CRRT provides improved chance for renal recovery
- Goal should be to use CRRT for initial therapy in critically ill patients.
- Further studies needed to assess effect on outcomes stratifying for timing of intervention, indication and dose.

UC San Diego School of Medicine

Renal Replacement in the ICU



The CRRT Safety Net!

What is the Future of RRT for AKI?

- Technology Advances x Targeted Therapy x Timing x Therapy Delivery = Therapeutic Success

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