Nemours. Children's Hospital

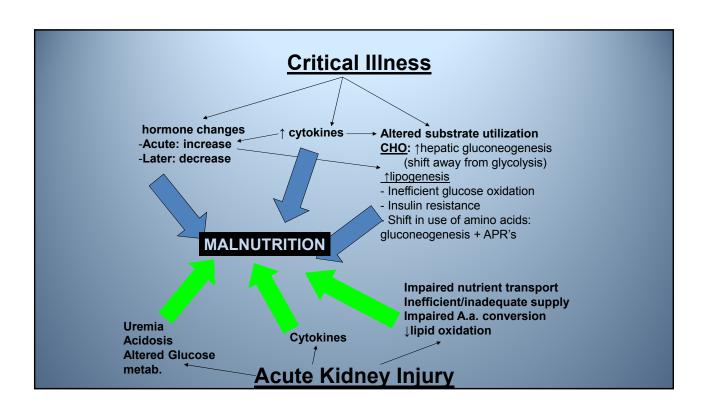
Nutritional Requirements for Critically III Children with Acute Kidney Injury

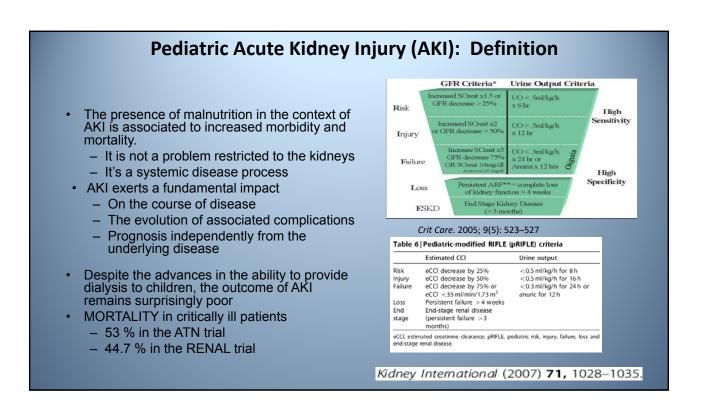
NKF- 15th Annual Renal Professionals Forum

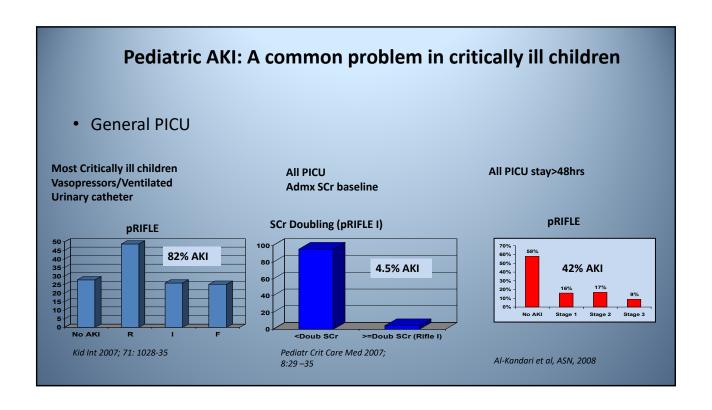
Carlos E. Araya, MD
Pediatric Nephrology
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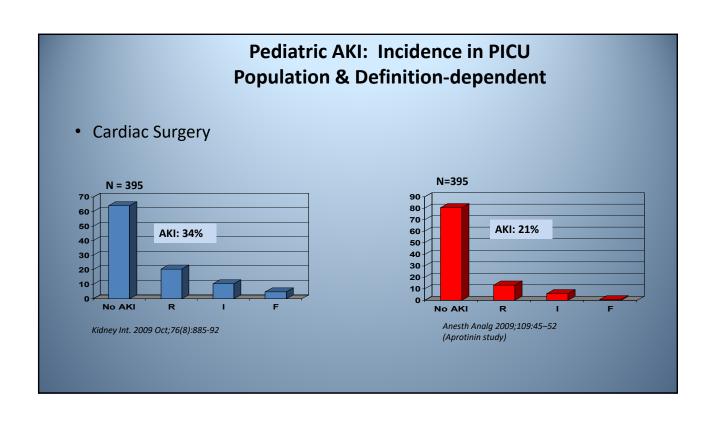
Nutritional Concerns in the Acute Phase of Critical Illness

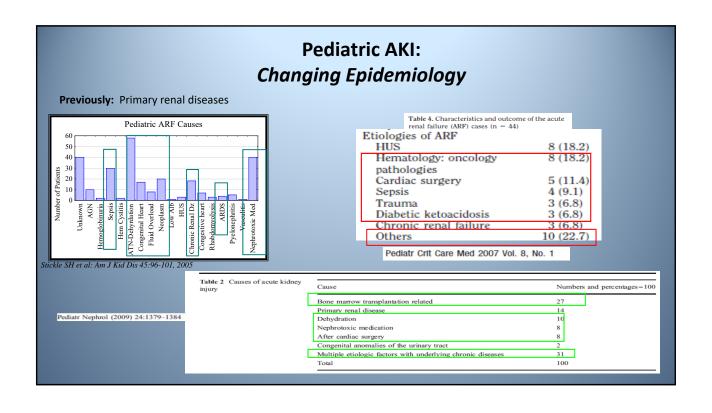
- Critically ill patients commonly have anorexia and may be unable to feed
- Energy deficit and lean-tissue wasting, associated with adverse outcomes
- The catabolic response to acute critical illness is much more pronounced than that evoked by fasting in healthy individuals
- Immobilization, pronounced inflammation and endocrine stress response
- Nutrition support is often deferred





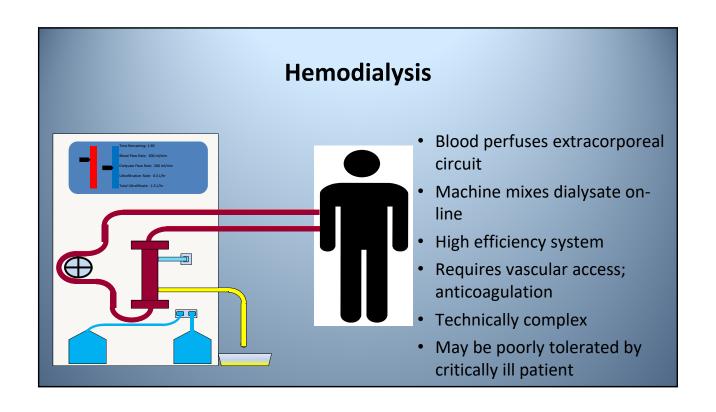


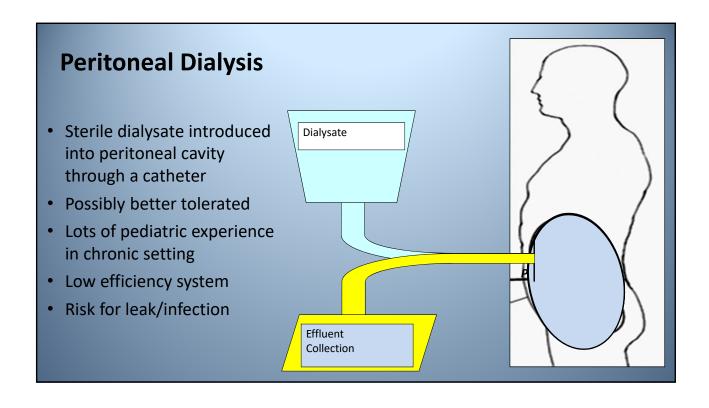


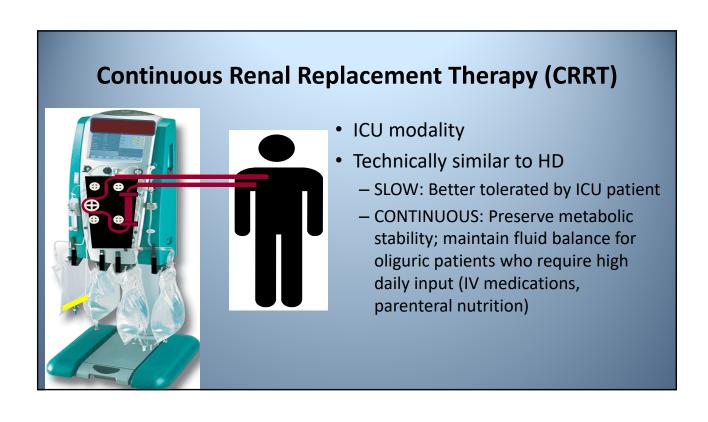


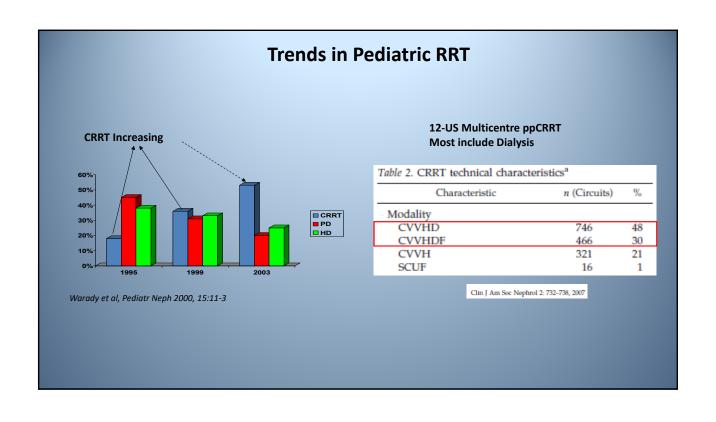
Management of AKI

- Largely supportive
- Aimed preventing of life-threatening fluid or electrolyte complications
- · Avoiding or minimizing further renal injury
- Severe AKI or milder AKI in association with severe fluid overload or solute imbalance may require renal replacement therapy (RRT)
- Providing appropriate nutrition to allow recovery from acute illness and renal dysfunction









Why CRRT in the Critically III with AKI?

- Reduces hemodynamic instability preventing secondary ischemia
 - Precise Volume control/immediately adaptable
 - Uremic toxin removal
 - Effective control of uremia, hyperphosphatemia, hyperkalemia
- · Acid base balance
 - Rapid control of metabolic acidosis
- · Electrolyte management
 - Control of electrolyte imbalances
- Management of sepsis/plasma cytokine filter
- Allows for improved provision of nutritional support

No Growth occurs during Acute Illness

Focus: Prevent Malnutrition

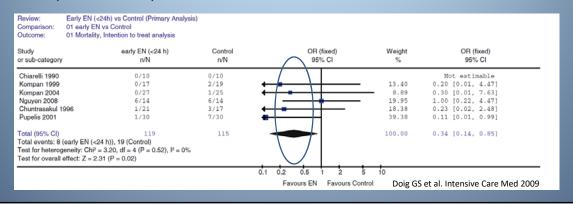
Children at Risk:
High basal rate of metabolism
Limited reserves
Baseline poor nutrition

Uremia and acidosis
Altered renal Amino Acid metabolism, lipid metabolism,
Fluid and Solute Clearance,

↑Losses from Renal Replacement Therapy

Initiation of Nutrition in the Acute Phase of Critical Illness

- Is it beneficial to initiate early feeds in the acute phase of critical illness?
- Meta-Analysis, 6 small trials, 234 patients
- Survival benefit with immediate initiation (24 h) of enteral nutrition as compared to delayed initiation



Review of Energy Needs and Utilization of Fuel

- Prospective observational study
 - a) Intakes of calories and protein recorded. Balance calculated by subtracting actual intake from RDA, over a max of 14 days.
 - b) Patients were evaluated also at discharge, 6 weeks and 6 months following discharge

Anthropometric parameters: Wt, Ht, OHC, MUAC, CC, BSF, TSF

24 % Undernourished on Admission

Mean Energy deficits	Mean Protein deficits;
27 kcal/kg – Preterm neonates	0.6 g/kg/day – Preterm
20 kcal/kg – Term neonates	0.3 g/kg/day – Term Newborns
12 kcal/kg – Older children	0.2 g/kg/day – Children

6 months follow up, almost all children had recovered their nutrition status.

Hulst J et al.Clin Nutr 2004;23:223-32 & 1381-9

Malnutrition in PICU population with AKI

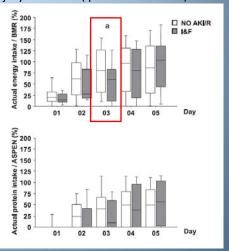
Retrospective Review: all PICU admissions over an 8 month period Kyle UG et

Kyle UG et al Clin J Am Soc Nephrol, 2013

- ☐ Incidence of Malnutrition was 20% in PICU population
- ☐ Incidence of Malnutrition was 33% in PICU Patients with AKI- Injury or Failure (pRIFLE Definition)

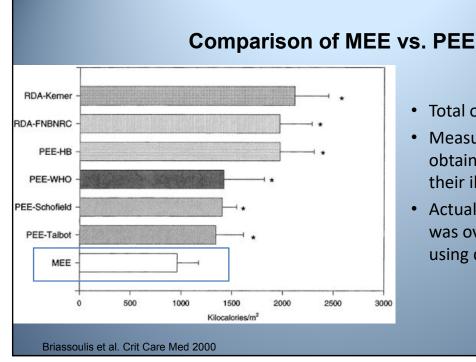
	% (n)	% (n)	OR (CI)	P
Acute malnutrition	Normal	Moderate/severe	192.5	
No AKI	86.3 (88)	13.7 (14)	1	
Risk	72.7 (32)	27.3 (12)	2.4 (0.99-5.6)	0.05
Injury/failure	66.7 (14)	33.3 (7)	3.1 (1.1-9.1)	0.03
Chronic malnutrition	CONTRACTOR	444.07.20440		
No AKI	82.4 (84)	17.6 (18)	1	
Risk	63.6 (28)	36.4 (16)	2.7 (1.2-5.9)	0.02
Injury/failure	76.2 (16)	23.8 (5)	1.5 (0.5-4.5)	0.51
PRISM III	≤6	>7		
No AKI	71.2 (74)	28.8 (30)	1	
Risk	52.3 (23)	47.7 (21)	2.3 (1.1-4.7)	0.03
Injury/failure	38.1 (8)	61.9 (13)	4.0 (1.5-10.7)	0.01
PELOD	≤21	>22		
No AKI	98.0 (100)	2.0(2)	1	
Risk	93.2 (41)	6.8 (3)	3.7 (0.6-22.7)	0.17
Injury/failure	81.0 (17)	19.0 (4)	11.8 (2.0-69.3)	0.01
Hospital LOS	≤14	>15		
No AKI	61.8 (63)	38.2 (39)	1	
Risk	52.3 (23)	47.7 (21)	1.5 (0.7-3.0)	0.29
Injury/failure	33.3 (7)	66.7 (14)	3.2 (1.2-8.7)	0.02
Survival	Alive	Died		
No AKI	97.1 (99)	2.9(3)	1	
Risk	100 (44)	0 (0)		
Injury/failure	85.7 (18)	14.3 (3)	5.5 (1.0-29.4)	0.05

Moderate/severe wasting is weight for age <2 z-scores below normal. Moderate/severe stunting is height for age <2 z-scores below normal, using the 2000 Centers for Disease Control and Prevention growth charts. OR, odds ratio; Cl, confidence interval; PRISM III, Pediatric Risk of Mortality Score; PELOD, Pediatric Logistic Organ Dysfunction; LOS, length of hospital stay.



Energy Expenditure in Critically III Children

- What are the energy requirements for critically ill patients?
- The nutritional requirements and the nature of substrate utilization in critically ill children have not been well defined.
- · In some critically ill adults
 - Hypermetabolic state occurs during critical illness
 - Energy expenditure is significantly greater than that in the normal resting nonstressed state
- Extrapolating from adult studies
 - Energy requirements in critically ill children can be estimated by adding a stress-related correction to the resting energy expenditure
 - There are several published formulas



- Total of 37 patients
- Measurements were obtained within 24 hrs of their illness or injury
- Actual energy expenditure was overestimated by using current formulas

Energy and Substrate Use in Acute Illness

- Coss-Bu helped define the metabolism of children during acute illness- Normal metabolic or hypermetabolic
- Hyper metabolic was defined as a state when the MEE at rest by indirect calorimetry was >10% above the predicted energy requirements
- The average energy given to the children was 0.25 MJ/kg/day (55kcal/kg/d)
- Measurements were obtained on average 12 days after admission

	Normal Metabolic (n = 14)	Hypermetabolic (n =19)
mREE (MJ/Kg/d)	0.16 +- 0.05 (38 kcal/kg/day)	0.28 +- 0.1 (66 kcal/kg/d)
Fat Oxidation (mg/min)	22 +-29	27+- 70
npRQ	1.21	0.86
	Coss-	Bu et al <i>Am J Clin Nutr</i> 2001

Energy Expenditure in Acute Critical Illness

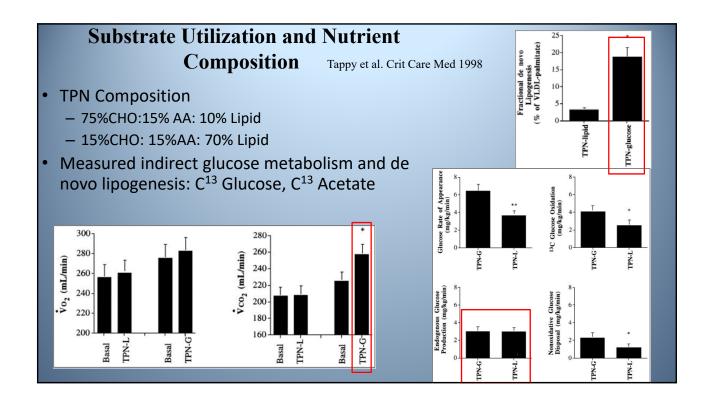
- Energy requirements depend on the phase of the illness
 - Acute phase vs convalescent phase
- The incidence of hypermetabolism is low in the acute phase
- Energy expenditure predicted by using RDA or specific formulas overestimates the actual energy expenditure in the acute phase of illness.
- It is not clear if providing a caloric intake greater than the MEE is clinically detrimental or beneficial in children.

Metabolic Fuel Changes during AKI and Acute Critical Ilness

How should we distribute the calories provided?

Fuel Substrate Changes in Acute Illness:

- 1. ↓ Carbohydrate Utilization : ~ 4 mg/kg/min of Glucose
- 3. Protein Catabolism to supply gluconeogenesis and hepatic acute phase proteins



Lipid Metabolism in Acute Critical Illness

- During starvation:
 - Reduction in insulin and increase in glucagon secretion
 - Mild sympathetic activation stimulates hormone sensitive lipoprotein lipase to increase the release of FFA from adipose tissue.
 - Much of the excess FFAs are converted by the liver to ketone bodies
- Early phase of Critical Illness: 个 FFA Utilization Occurs
 - the nutritional hormones are no longer substrate controlled
- Yet in Acute Kidney Injury
 - Impaired Lipolysis: Lipase Activity ~50%
 - ↓ Lipoprotein Lipase
 - → Hepatic Triglyceride Lipase

Lipid Metabolism in AKI

Impaired Lipolysis:

Lipase Activity ~50%

Altered Lipid Profile:

个 LDL and VLDL

↓ Cholesterol and HDL-Cholesterol

Cholesterol: Conditional Essential Nutrient in AKI?

- · Ten adults with normal lipemia
- Standard 20% lipid emulsion and 20% lipid emulsion with 4g/L of free cholesterol
- Results:
 - Reduced Plasma Triglycerides with reduced plasma ½ life and ↑ total body clearance
 - Fraction of Lipid Oxidation Improved
- No studies to date evaluating if this free cholesterol would show improved TG clearance and utilization in patients with AKI.

Druml et al, Wien Klin Worchenschr 2003;115/21-22:767-774

Type of Lipid Used in Nutritional Formulations

- May affect inflammation: n-3 fatty acids have antiinflammatory effects while n-6 fatty acids are proinflammatory
- OMEGA study
 - -N = 272 patients
 - Enteral administration of n-3 fatty acids plus antioxidant supplement
 - No benefit in mortality and other outcomes
- Parenteral administration of different fatty acids
 - No benefit with the administration of fish oil based FA (n-3)
 - No effect on outcomes with the use of olive oil based FA (n-6)

Acute Kidney Injury and Catabolic Stress

- Physiologic changes due to AKI and critical illness cause derangements in substrate metabolism and lead to catabolic state, hypoalbuminemia, loss of lean body mass
- Muscle protein catabolism and atrophy occur as a result of:
 - Systemic inflammation
 - Oxidative stress
 - Insulin resistance
 - Metabolic acidosis
 - Uremic toxic metabolic impairment
- Hepatic acute phase protein synthesis rather than anabolism
- Maintenance of protein balance in such conditions requires that at least adequate energy and protein intake be provided during acute illness.

Protein Catabolism and Nitrogen Balance

- Adult Studies:
 - Protein Catabolic Rate ~ 1.4 1.7 g/kg/d
- Pediatric Studies:
 - Urea Nitrogen Appearance ~ 185- 290mg/kg/d
 - Protein Catabolic Rate ~ 1.1- 1.8 g/kg/d
 - Amino acid loss on CRRT 11-12% of daily protein intake

Macias WL, et al. JPEN 1996 Chima CS, et al. JASN 1993 Kuttnig M, et al. Child Nephrol Urol 1991 Maxvold N, et al. Crit Care Med 2000

Protein Intake and ICU Outcomes

- Prospective Cohort Danish Study:
- N=113 Adults, Intubated, severe sepsis or >15% Burn
- Energy and Protein Intake, Nitrogen and Energy Balance was monitored

	Low Protein/AA Intake (53.8 g/d)	Medium Protein/AA Intake (84.3 g/d)	High Protein/AA Intake (114.9 g/d)
K-M Survival Probability on Day 10	49%	79%	88%

Only ↑ Protein Provision was Associated with ↓ Mortality:

HR (Risk of Death vs time) \downarrow 2% for every additional gram of protein provided.

No Associated found Between Hazard of Mortality and Energy

Allingstrup MJ et al. Clin Nutr 2012;31:462-468

Protein Intake and Outcomes in ICU Patients on RRT

N=50 Mechanically Ventilated, CRRT Patients with APACHE 26 ± 8

Daily Energy (kcal) kept constant and determined by IC when available or Schofield Equation. Three sequential isocaloric protein-feeding regimens were provided

	Control: N=10	Intervention: N=40
Protein Diet	2g/kg/d x 6 days	1.5 - 2.0 - 2.5 g/kg/d Escalation at 48° Intervals
Nitrogen Balance	Negative Over Time	Positive over time in Response to ↑ Protein Support
Energy Expenditure (IC): In	creased by 56±24 cal/day ove	er the study period

Nitrogen balance was associated with outcome

For every 1g/d increase in nitrogen balance, the probability of survival increased by 21%. (OR 1.21; 95% CI 1.017-1.444)

Enterally fed patients had a better outcome

Scheinkestel CD et al. Nutrition 2003;19:909-16

Nutrition and CRRT

Can Nitrogen Balance be achieved in AKI patients on CRRT?

- Nitrogen metabolism was studied in two cohorts
- Patients received equal amounts of calories
- The higher protein diet improved nitrogen balance and could be safely administered to AKI patients on CRRT

	Moderate Protein Intake	High Protein Intake
Protein Intake	1.2 g/kg/d	2.5 g/kg/d
Nitrogen Balance	-5.5 g N/d	-1.9 g N/d
Positive Nitrogen Balance during a 24h period	36.7%	53.6%
Mean Plasma Urea	18 mmol/L	26.6 mmol/L
Survival	31.1%	37.5%

Bellomo et al Renal Failure 1997

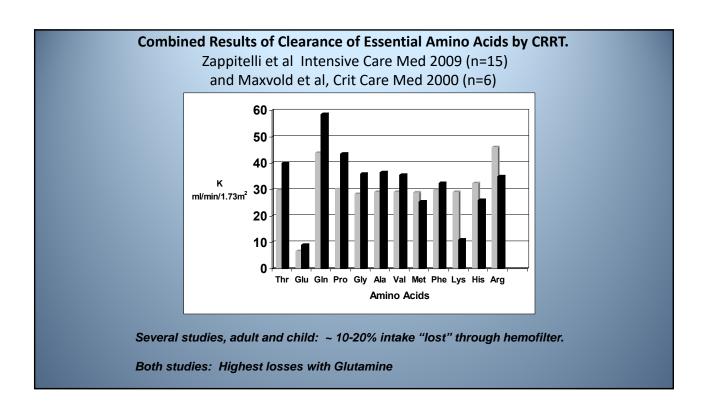
Protein Losses on Renal Replacement Therapy: Slow IHD, PD, CVVHD

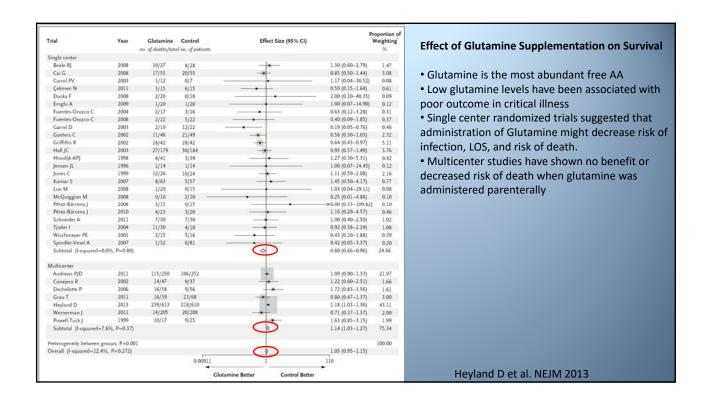
	IHD (Qb=80ml/min, D=1.8L/hr x 12 hr, SA=0.7m2	PD:IPD for 10hr/day: Acute PD for 36hrs : CAPD for 24hr/day	CVVHD(Qb=150mL/min, D= 1-2L/hr,UF= 0.67L/hr, SA=0.5m2
AA/Protein loss (grams)	6g/day	IPD=12.9 g/d Acute PD=23.3 g (15.5g/d) CAPD= 8.8 g/d	12g/day
% AA intake lost via RRT	16%	NA	5-12%
Diet prescription AA/Protein NP kcal [CHO: Lipid]	40 g/day 2000-2400 kcal/d	NA	2.5g/kg/day 35kcal/kg/day [60:40]

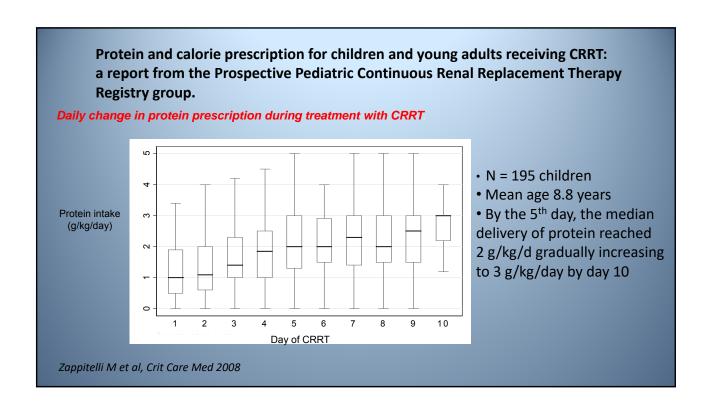
Kihara M et al. Intensive Care Med 1997;23:110-3 Blumenkrantz MJ et al. Kidney Int 1981;19:593-602 Bellomo R et al, Int J Artif Organs 2002; 25:261-8

Protein Losses on RRT

	Davenport (1989)	Davies (1991)	Bellomo (2002)	Maxvold (2000)
Calorie Intake NPkcal (CHO:Fat)	1450 kcal (~70:30)	2000-2400 kcal	2100 kcal (60:40)	1.25 x mEE (70 : 30)
AA Intake g/day	60 g AA (1L Vamin9)	60:84:112 AA 1L of Vamin9:14:18	2.5g/kg/day (1 L Synthamin 17)	1.5g/kg/day Aminosyn II
AA Loss/day	2.4g/d : 7.9g/d	NA	~ 12g/day	CVVH:12.5g/d/1.73m2 CVVHD:11.6g/d/1.73m2
% Dietary AA Loss	13%	12%	~ 12%	~11.5%
N2 Balance: g/day	NA	NA	-1.8g/d	CVVH: -3.68 g/d CVVHD: -0.44 g/d
RRT Prescript: UF rate: L/hr HF SA = m2	0.5L/hr : 1L/hr 0.6 m2	UF:0.5L/hr: D:1L/hr : D2L/hr 0.43m2	UF:0.67L/hr D :1-2L/hr 0.5 m2	UF : 2L/hr D : 2L/hr 0.3 m2
	Davenport A et al, Blood Purif 1989;7:192-6 Davies SP et al, Crit Care Med 1991;19:1510-5 Bellomo R et al, Int J Art Organs 2002;25:261-8 Maxvold N et al Crit Care Med 2000;28:1161-5			







Trace Metal and Folate CRRT Clearance in Children

- Should we replace micronutrients?
- Trace metal deficiencies have been implicated in lymphocyte, platelet, antioxidant dysfunction and poor wound healing
- Micronutrients that are water soluble, non protein bound and relatively small (<10,000Dalton) are readily cleared
- Selenium, chromium and folate clearances were high
- Folate level decreased significantly by Day 5

	K Day 2 (ml/min/1.73 m ²)			Serum concentrations		
	(111/11111/1./3 111)	(III/IIIII/1./3 III)	Initiation	Day 2	Day 5	Reference range ^a
Selenium Copper Chromium Zinc Manganese Folate	10.1, 9.5 (74, 13.3) 0.4, 0.3 (0.2, 0.6) 24, 25 (22, 32) 4.2, 3.2 (2.2, 4.6) 9.0, 4.6 (0.3, 8.5) 29, 16 (14, 22)	8.6, 7.2 (6.5, 11.4) 0.5, 0.4 (0.3, 0.5) 25, 26 (19, 29) 4.0, 2.9 (2.3, 4.2) 38.2, 5.1 (0.2, 20.2) 16, 16 (13, 18)	55, 49 (39, 66) 88, 87 (69, 100) L ^b 2, 2 (1, 2) 66, 53 (32, 79) L ^b 9, 4 (2, 6) H ^b 16, 12 (7, 23)	61, 59 (46, 70) 110, 106 (80, 140) 2, 2 (2, 3) 68, 61 (49, 79) 8, 3 (2, 7) H ^b 10, 9 (6, 14)	64, 63 (45, 86) 104, 103 (95, 128) 2, 2 (2, 3) 76, 68 (50, 101) 8, 3 (2, 3) H ^b 8, 7 (6.4, 7.9)	23–190 (µg/l) 90–190 (µg/dl) 0–2.1 (µg/l) 60–120 (µg/dl) 0–2 (µg/l) 5.4–40 (ng/l)
			Zappi	telli M, et al, Intens	sive Care Med 2009	

Insulin - Anabolic hormone for Muscle Metabolism: Catabolic State: Insulin effect on MPS (AA Uptake) Insulin effect on MPB (Ubiqutin-Proteasome) Ikizler, TA. J Renal Nutr 2007; 17:13-16 Imbalance of MPB with MPS result in PEW Reid M, Li YP. Resp Res 2001; 2:269-272

Benefit of Insulin Therapy in the Critically III: insulin dose vs glycemic control Risk of Death- BG <110, 110-150, >150 Is it feasible and safe to maintain normoglycemia? P = 0.0009 Cumulative Hazard (%) (in hospital death) Randomized to insulin infusion or conventional approach Normoglycemic Control [80-110 mg/dl] ↓ Polyneuropathy ↓ Bacteremia **↓** Inflammation Anemia **Reduction of Mortality** 100 150 Days after inclusion Van den Berghe G, et al. Crit care Med 2003

Nutrition in Children with AKI		
Nutritional parameter		
Nutrition modality	-Early enteral feeding is beneficial. Some patients may require parenteral nutrition supplement	
<u>Energy</u>	35 to 60 kcal/kg/day (0.15-0.27 MJ/kg/day) 25-35%Carbohydrate: 35-45% Lipid (Insulin as needed for Hyperglycemia) 25-40% Protein	
<u>Protein</u>	2 - 3 g/kg/day with AKI (Increase intake if on High flow CRRT (by 20%)	
<u>Lipids</u>	No recommendation on the type of formulation that should be provided	
<u>Vitamins</u>	Daily recommended intake (± replacement) Monitor serum folate, water soluble vitamin levels	
Trace elements	Daily Recommended Intake	
Monitoring	MEE, Nitrogen Balance, Glucose, lytes, TG, Vitamins, Trace elements	
Conditional Nutrients??	Glutamine, free Cholesterol	

Questions?
Thank You!