PROVISION OF MACRONUTRIENTS AND MICRONUTRIENTS IN ACUTE KIDNEY INJURY

K. Matysiak-Lusnia (PL)
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Provision of macronutrients and micronutrients in acute kidney injury

Katarzyna Matysiak-Lusnia, MD, PhD
Senior Assistant, Medical University of Wroclaw, Clinic of Anaesthesiology and Intensive Therapy, Poland
Enteral and Parenteral Outpatient Clinic, Voyevodin Hospital, Jelenia Gora, Poland
Home Hospice and Palliative Care Ward, Voyevodin Hospital, Jelenia Gora, Poland
Disclosures

- Nutricia
- Baxter
- Nestle
- Fresenius Kabi
- BBraun
Agenda

- AKI as a complex inflammatory syndrome
- Influence of AKI on macronutrients metabolism
- Influence of AKI on vitamins, trace elements and electrolytes
- RRT: nutrients requirements
- Take-home messages
AKI: an abrupt and sustained reduction in kidney function

<table>
<thead>
<tr>
<th>Class</th>
<th>Serum creatinine or GFR criteria</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk (stage 1)</td>
<td>Serum creatinine x 1.5 or GFR decreased by &gt; 25%</td>
<td>&lt; 0.5 ml/kg/h for 6-12 hours</td>
</tr>
<tr>
<td>Injury (stage 2)</td>
<td>Serum creatinine x 2 or GFR decreased by &gt; 50%</td>
<td>&lt; 0.5 ml/kg/h for &gt;12 hours</td>
</tr>
<tr>
<td>Failure (stage 3)</td>
<td>Serum creatinine x 3 or serum creatinine ≥ 4 mg/dl</td>
<td>&lt; 0.3 ml/kg/h for &gt;24 hours or anuria for ≥12 hours</td>
</tr>
</tbody>
</table>

Stage       Serum creatinine                                                                                                                                                                                                 |
--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
1'           An increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l), or an increase to more than or equal to 150-200% (1.5 to 2-fold) from baseline                                                 |
2            An increase in serum creatinine to more than 200-300% (> 2- to 3-fold) from baseline                                                   |
3”           An increase in serum creatinine to more than 300% (> 3-fold) from baseline, or serum creatinine of more than or equal to 4 mg/dl (≥ 354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l) | Less than 0.3 ml/kg/hour for 24 hours or anuria for 12 hours |
• Acute kidney injury (AKI) occurs in 39 - 57% of intensive care unit (ICU) patients, and 6–14% of ICU patients are treated with renal replacement therapy (RRT)

• Patients with RRT-treated AKI have a 90-day mortality of 50–60% and a 5-year risk of end-stage renal disease (ESRD) of > 10%

Hoste EA. Intensive Care Med. 2015;41:1411
De Corte W. Crit Care. 2016;20:256
AKI in hospital setting

- ICU-s: 10-30%

- Other wards (3-10%): mostly volume overload refractory to diuretics, drug toxicity, contrast nephropathy, mild-to-moderate-oliguric forms of AKI

MOF

Mortality ↑

Morbidity ↑

Lameire N. Lancet 2005; 365: 417
PEW in AKI/critical illness: protein catabolism

- Insulin resistance
- Ureaemia/toxins
- Catabolic hormones
- Acute phase reaction (SIRS): cytokines
- Inadequate supply
- Protein synthesis ↓
- RRT: loss of substrates
- Ubiquitine-proteasome system (proteases)
- Drugs
- Metabolic acidosis
PEW in AKI: protein metabolism

- Tissue utilization of exogenous aa ↓
- Aa oxidation ↑
- Aa transport to tissues (eg muscles) ↓
- Serum and tissue aa pattern profoundly altered: phenylalanine, methionine, taurine, cysteine ↑, valine, leucine ↓
- Non-essential aa become conditionally essential: tyrosine, arginine
- Inadequate conversion of phenylalanine to tyrosine

Btaiche IF. Pharmacotherapy 2008; 28: 600
Kidneys in AKI: glucose metabolism

- Insulin resistance and hyperglycemia
- Peripheral glucose utilization in insulin-dependent tissues (fat and muscles) is decreased
- Hepatic gluconeogenesis from AA and lactate ↑ (cortisol, catecholamines, glucagone)
- Exogenous glucose supply doesn’t suppress hepatic gluconeogenesis
Kidneys in AKI: glucose metabolism

- Reduced renal clearance of insulin, decreased gluconeogenesis by the kidney

- Risk of hypoglycemia↑ (more frequently observed during intensive insulin therapy in AKI)

- Glucose 110-149 mg%/dL (KDIGO 2012)

- Direct detrimental and toxic influence of hyperglycemia on tissues independent of insulin: on nervous cells, immune system (glycation)

- **DYSGLYCEMIA**: average blood glucose concentration, glycemic variability and incidence of hypoglycemia is higher in critically ill with AKI

Mackenzie IM. Intensive Care Med 2011;37:435
Dickerson RN. Nutrition 2011;27:766
Kidneys’ role in lipid metabolism

- β-oxidation of fatty acids
- De-novo synthesis of FA and cholesterol
- Degradation of ketone bodies (*ketolysis*)
- Synthesis of carnitine: indispensable for transport of FA to mitochondria for oxidation
- Activation of glicerol to glicerol-3-phosphate (kidney has active glicerol kinase enzyme)
Lipid metabolism in AKI

- Lipolysis in peripheral adipose stores
- Incomplete oxidation of FFA (hyperglycemia/hyperinsulinemia)
- More FFA re-estrified and increased hepatic triglyceride production and secretion in lipoproteins
- Hipertriglyceridemia due to reduced lipoprotein lipase activity and tissue uptake of remnant particles
- Reduced clearance of exogenous lipids
- Decreased lipid clearance (up to 50%): hypertriglyceridemia

Lipids during CRRT

- High molecular weight and lack of water solubility preclude lipid elimination by CRRT. Lost in negligible amounts.

- May provoke early packing or clotting of filters.

- Triglycerides accumulate: routine level checking mandatory.
Goal-directed nutrition in AKI

- Protein-Energy Wasting (PEW)
- Lean body mass ↑
- Nutritional status ↑
- Complications ↓
- Wound healing ↑
- Immune function ↑
- Mortality ↓
- Antioxidant activity ↑
- Inflammation ↓
- Endothelial function ↑
- Nutritional status ↑
- Lean body mass ↑
- Complications ↓
- Wound healing ↑
- Immune function ↑
- Mortality ↓
- Antioxidant activity ↑
- Inflammation ↓
- Endothelial function ↑
Phases of critical illness

1. **Solid bold line**: TEE

2. **Grey bold line**: adapted endogenous energy production

3. **Dotted bold line**: early energy administration

4. **Thin line**: combined endogenous and exogenous energy administration

Oshima T. Clinical Nutrition 36 (2017) 651
A: CO2/O2 exchange
B: immunologic activation/heat loss
C: protein/glucose/lactate exchange
D: citrate
Citrate is a key energy substrate for cells
Citrate is metabolized in the Krebs cycle
5 mmoles of citrate (1 gr) are 3 Kcal
Citrate load to the patient during RRT with citrate is highly variable
→ citrate as a potential, hidden calorie source (from 300 to 1000 kcal/day depending on the RRT modality and citrate protocol used)

Regional Citrate Anticoagulation for RRTs in Critically Ill Patients with AKI

Santo Morabito,* Valentina Pistolesi,* Luigi Tritapepe, † and Enrico Fiaccadori ‡

Citrate is increasingly utilized, with excellent results, for regional anticoagulation of the circuit in RRT

CRRT provokes a heat loss of approximately 1,000 kcal/day, which must be considered into the energy balance account.

Neutral environment temperature: 27-29 °C

Robert R. Ann Intensive Care 2012;2:40
Regarding the different modalities (CVVH, CVVHD, CVVHDF etc.), differences are tiny as long as the dose is the same amongst the various modalities.
Energy requirements

• IC measures VO2 and VCO2 based on the assumption that gas exchange as a result of nutrient consumption and energy production is represented by the breath gas composition

• IC has not been validated and even is considered to be contraindicated during CRRT (AARC, 2004)

• During CRRT the expiratory concentration of CO2 increases, which does not result from increased metabolism.

• VCO2 measurements are influenced by CRRT because CO2 is exchanged during the blood purification process

• CO2 exchange also depends on type of pre- and/or postdilution fluid(s)

• CO2 dissolves in different forms with dynamic but unpredictable impact on VCO2

• Heat loss on REE caused by extracorporeal circulation during CRRT

• Rate of dialysis, the rate of ultrafiltration, the type of filters used („dialytrauma concept“)

• Elevated serum concentration of the proinflammatory cytokine interleukin-6 is associated with increased energy expenditure
Maya Hites.
Advanced Drug Delivery Reviews, Volume 77, Nov 2014, 12
Size of molecules cleared during CRRT

- **Large**: Convection or adsorption
  - Albumin (55,000 - 60,000)
  - TNFα (17,500)
  - Inulin (5,200)

- **Medium**: Rather convection than diffusion
  - Glucose (180)
  - Uric acid (168)
  - Creatinin (113)

- **Small**: Rather diffusion than convection
  - Phosphate (80)
  - Urea (60)
  - Potassium (35)
  - Phosphorus (31)
  - Sodium (23)

Size of molecules in daltons
CRRT: losses

- In CRRT, about 0.2 g amino acids are lost per liter of filtrate, amounting to a total daily loss of 10–15 g amino acids. That is true for UF efficiency of 10-15 ml/kg.

- In addition, 5–10 g of protein are lost per day, depending on the type of therapy and dialyzer membrane.

- Amino acids are the molecules of a relative low molecular weight, ranging from 89 Da for alanine to 214 Da for tryptophan.

- During CVVHD (blood flow rate: 100-175 ml/ min, dialysate flow rate-2 l/h), 17% of aa administered intravenously are lost on average (range 13–24%).

- Tyrosine: esp susceptible to migration into the ultrafiltrate: lost during the procedure at 87% of the administered dose!
CRRT: hidden calories sources

- Lactate as a buffer
- Citrate as a anticoagulant
- Glucose in citrate solutions and dialysis fluids

- Risk of overfeeding
(C)RRT: composition of macronutrients

- At least 1.5 g/kg/day of protein (0.25 gN/kg/d); up to 1.7-1.8-2.0-2.5 g/kg/day if CRRT
- Lipids: about 30-35% of total non-protein energy supply
- Lipids in PN: 0.8-1.2 g/kg/day
- Energy needs should be measured by IC. If IC is not available 20-30 kcal/kg/day should be prescribed

KDIGO. Clinical practice guidelines for acute kidney injury. Kidney Int 2012 (suppl. 2);1-138
Protein catabolic rate in critically ill patients with AKI on RRT

Protein catabolic rate (nPCR), g/kg/day

Macias WL et al, J Parent Ent Nutr 1996; 20:56

Fiaccadori E et al., Nephrol Dial Transpl 2005; 20:1976
For non-catabolic AKI patients with milder non-oliguric forms of the syndrome not needing RRT and who are likely to regain renal function in a few days (drug toxicity, contrast nephropathy etc.), lower protein intakes (up to 0.8 g/kg/day) will suffice for short periods of time, combined with adequate calorie intakes (20-30 kcal/kg/day).
Electrolites during CRRT

- Hipokalemia: present in 5 - 25% of patients; usu inadequate supplementation; mainly if hypervolemia is a reason for CRRT

1. Potassium-rich replacement fluids
2. Administration of potassium supplements

Prowle JR. Nat Rev Nephrol 2010; 6: 521
Electrolites during CRRT

- Hipophosphatemia: 10.9 - 65% of patients

1. Oxygen transport and energy transfer (ATP regeneration)
2. Fluids containing physiological phosphate concentrations
3. Intravenous bolus or enteral supplements
4. Levels should be controlled daily during CRRT
5. Not only the dose but also the duration of CRRT does affect phosphate levels (HD<CRRT in spite of more efficient clearance)
6. Both hipo- and hyperphosphatemia are deleterious and associated with increased mortality (U-shape curve)

Prowle JR. Nat Rev Nephrol 2010; 6: 521
Ratanarat R. Blood Purif 2005; 23: 83
Calabrese EJ. Annu Rev Publ Health 2001;22:15
Electrolites during CRRT

• Hyperphosphatemia and hyperkaliemia:
  1. Accelerated by protein catabolism
  2. Massive intracellular necrosis (e.g. severe bowel ischemia, rhabdomyolysis)
  3. Hyperphosphatemia can cause renal injury, through deposition of calcium phosphate in tubules

Agrawal N. Am J Transplant 2009; 9: 1685
Electrolites during CRRT

• Hypomagnesemia: < 3%

1. Corrected with daily administration of 2 - 4 iv magnesium salt boluses

2. Enteral magnesium supplementation problematic: direct osmotic effect on the distal small bowel and laxative action

3. Large (20 mmol+) dose of iv magnesium is rapidly excreted in the urine even in severe Mg deficiency

4. Smaller multiple (6-12 mmol) doses more successful

• Sometimes a correction of vitamin D level is enough
Trace elements

• Selenium, chromium, copper and zinc can be loss from plasma by convection/ultrafiltration in the effluent

1. Inflammatory response: redistribution of trace elements from plasma to other tissues
2. Dilution of the circulating compartment by resuscitation fluids
3. Feces, drains
4. Inadequate intakes

• Alteration of the endogenous antioxidant defenses

Berger MM. Am J Clin Nutr 2004;80:410
Trace elements

• During prolonged CRRT (> 2 weeks) copper and selenium levels should be monitored

• Copper deficit results in life-threatening bradycardia and the alteration of lipid metabolism with severe hypertriglyceridemia

• Selenium doses in excess of DRI should be avoided in case of renal failure without RRT

Ben-Hamouda N. Nutrition. 2017 Feb;34:71
Water-soluble vitamins

- Highly removed by CRRT
- Recommendations for daily supplementation:
  - 100 mg vitamin B1
  - 2 mg vitamin B2
  - 20 mg vitamin B3
  - 10 mg vitamin B5
  - 200 mg biotin
  - 1 mg folic acid
  - 4 μg vitamin B12
  - 250 mg vitamin C

Clin Nutr 2009; 28: 401
Vitamin C

- Eliminated by both diffusion (dialysis) and convection (filtration)
- During hemodiafiltration, diffusion is responsible for two thirds of the vit. C loss whereas convection accounts only for one third

Morena M. Nephrol Dial Transplant. 2002;17:422
Fat-soluble vitamins

- Vitamins E and K: 10 IU/day and 4 mg/week
- Vitamin A: must be reduced to compensate for deficient retinol degradation
- Not every MV product has vitamin K
Other nutrients

• Carnitine: severe alterations of lipid and energy metabolism at the mitochondrial level

Bonafé L. Curr Opin Clin Nutr Metab Care 2014;17:200
Consensus recommendations for daily micronutrient administration

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Consensus recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A/retinol</td>
<td>3300–3500 IU (990–1050 μg RE)</td>
</tr>
<tr>
<td></td>
<td>200 IU (5 μg)</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Individual assessment</td>
</tr>
<tr>
<td>Vitamin D/cholecalciferol</td>
<td>3–6 mg</td>
</tr>
<tr>
<td>Vitamin E/alpha tocopherol</td>
<td>3.6–5 mg</td>
</tr>
<tr>
<td>Vitamin K/phytomenadione</td>
<td>40–47 mg</td>
</tr>
<tr>
<td>Vitamin B₁/thiamin</td>
<td>15–17 mg</td>
</tr>
<tr>
<td>Vitamin B₂/riboflavin</td>
<td>3–6 mg</td>
</tr>
<tr>
<td>Vitamin B₃/niacin</td>
<td>5–6 μg</td>
</tr>
<tr>
<td>Vitamin B₅/pantothenic acid</td>
<td>400–600 μg</td>
</tr>
<tr>
<td>Vitamin B₆/pyridoxine</td>
<td>110–200 mg</td>
</tr>
<tr>
<td>Vitamin B₁₂/cobalamin</td>
<td>60 μg</td>
</tr>
<tr>
<td>Vitamin B₉/folic acid</td>
<td>39–100 μmol</td>
</tr>
<tr>
<td>Vitamin C/ascorbic acid</td>
<td>(2.5–6.5 mg)</td>
</tr>
<tr>
<td>Biotin</td>
<td>4.7–9.6 μmol</td>
</tr>
<tr>
<td>Zinc (Zn)</td>
<td>(300–610 μg)</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>0.25–1.25 μmol</td>
</tr>
<tr>
<td>Selenium (Se)</td>
<td>(20–100 μg)</td>
</tr>
<tr>
<td>Manganese (Mn)</td>
<td>1–1.8 μmol</td>
</tr>
<tr>
<td>Iron (Fe)</td>
<td>(55–100 μg)</td>
</tr>
<tr>
<td>Chromium (Cr)</td>
<td>1–1.2 mg in those</td>
</tr>
<tr>
<td></td>
<td>recommending Fe</td>
</tr>
<tr>
<td>Molybdenum (Mo)</td>
<td>0.2–0.3 μmol</td>
</tr>
<tr>
<td>Iodine (I)</td>
<td>(10–15 μg)</td>
</tr>
<tr>
<td></td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

Renée Blauw. Parenteral Provision of Micronutrients to Adult Patients: An Expert Consensus Paper. JPEN, 2019
Take-home messages

• Not only as a part of parenteral nutrition but also to compensate for additional losses micronutrients should be given to replete/supplement: CRRT, extensive enteral losses, increased oxidative stress, insufficient enteral feeding, major burns, losses from surgical/traumatic wounds, gastrointestinal fistulae, resections

• Patients with several pathologies require special attention
References

5. www.espen.org
2. Dickerson RN. Increased hypoglycaemia associated with renal failure during continuous intravenous insulin infusion and specialized nutritional support. Nutrition 2011;27:766
6. AARC clinical practice guideline. Metabolic measurement using indirect calorimetry during mechanical ventilation. 2004 Revision&update. Respir Care 2004 sep;49(9):1073-9
9. KDIGO. Clinical practice guidelines for acute kidney injury. Kidney Int 2012 (suppl. 2);1-138
Thank you