This article focuses on the impact of fluid and nutrition administration on kidney function. It discusses the deleterious effects of accumulating fluid overload leading to kidney oedema and worsening kidney function, and provides advice on how to adapt nutrition in the different stages of AKI, with or without RRT. Finally, information on the cardio-abdominal-renal syndrome (CARS) is provided, since AKI seldom comes alone.

Introduction

It is important for a patient with chronic kidney disease that he or she knows what to eat in order to prevent further disease progression. Similarly, it may also be equally important for the ICU patient admitted with septic shock that we as ICU physicians adapt our treatment in order to prevent the development of AKI or its progression from an oliguric to anuric state.

Fluids and AKI

It is beyond the scope of this review to discuss the effects of different replacement and resuscitation fluids like crystalloids, starches or albumin on kidney function. Recent randomised controlled clinical trials (6S, CRYSTMAS and CHEST) could not demonstrate a benefit for colloids over crystalloids (Pemer et al. 2012; Guidet et al. 2012; Myburgh et al. 2012a). This re-opened the debate as to whether hydroxyethyl starches...
130/0.4 are safe to use, especially in septic patients with AKI (Haase and Perner 2012). Colloids seem to be related to increased risk for AKI and longer duration of RRT (Guidet et al. 2012; Schortgen et al. 2001; Cittanova et al. 1996; Brunkhorst et al. 2008). The VISEP study on the other hand did not show a statistical significant difference (Brunkhorst et al. 2008). The largest CHEST trial showed no difference in outcome between crystalloids versus colloids, but crystalloids were associated with less AKI and less RRT, although the risk for renal failure was the same (Myburgh et al. 2012b). It remains to be proven whether these observations can be extrapolated also to the newer balanced starches.

More important is the impact of fluid overload on end organ function (Malbrain et al. 2012, Malbrain and Van Regenmortel 2012). In patients with septic shock and capillary leak, fluid administration will lead to accumulation of second and third space fluids, especially if the patient does not transgress spontaneously from the ebb to flow phase of shock (Malbrain 2013). End-organ oedema may then lead to organ dysfunction, while the combination of ascites, intestinal oedema, and ileus may lead to increased intra-abdominal pressure (IAP), which in turn can worsen kidney function by reduction of renal plasma flow and decreased glomerular filtration rate (GFR) (De Laet, Malbrain et al. 2007). Even in the absence of overt intra-abdominal hypertension (IAH), renal interstitial oedema alone might impair renal function. As an encapsulated organ, the kidney is affected by fluid congestion and raised venous pressures with a disproportionate elevation in intracapsular pressure, which leads to a decrease in renal blood flow and GFR (Prowle et al. 2012). Many other studies and reviews focus on the same relation between fluid overload and IAH or AKI (Bouchard and Mehta 2009; Prowle and Bellomo 2013; Prowle and Bellomo 2010; Butcher and Liu 2012; Cordemans et al. 2012). After the initial early resuscitation phase a conservative fluid management strategy seems advocated (Murphy et al. 2009). No randomised controlled study exists to show that a positive fluid balance is beneficial in AKI or during acute illness in general. However, a recent meta-analysis showed consistent deleterious effects (on morbidity and mortality) of a positive cumulative fluid balance within the first week of ICU stay (Malbrain et al. 2012). Since the only way to give nutritional support is via the enteral or parenteral route, nutrition and fluid administration cannot be separated from each other.

**Nutrition and AKI**

- **Nutrition and Kidney Disease**

As the aetiology and severity of AKI is diverse and can be either prerenal vs renal vs postrenal, with or without pre-existing chronic kidney disease, with or without RRT, the recommendations for nutritional support can at best be described as open for discussion and debate. The Acute Dialysis Quality Initiative recommended expressing the severity of AKI with the RIFLE criteria (Bellomo et al. 2004), which assess the severity (risk of renal dysfunction, injury to the kidney, and failure of kidney function) and outcome (loss of function and end stage renal disease) in AKI.

The recommendations below are based on the ESPEN Guidelines and recent reviews (Cano et al. 2009; Cano et al. 2006; Toigo et al. 2000a, 2000b; Berbel et al. 2011; Fiaccadori and Cremaschi 2006; Fiaccadori et al. 2008).

- **Normal Energy Expenditure**

The human body should be seen as a metabolic engine that needs organic fuels. These fuels (lipids, carbohydrates and proteins) are combusted in combination with oxygen and produce heat, Kcal and waste. The energy yield differs from 9.1 kcal/g for lipids, 4 kcal/g for protein and 3.75 kcal/g for glucose. Normal nutritional requirements (daily energy expenditure) can be calculated by different formulas:

**BEE** (Basal Energy Expenditure) kcal/24 hr

- Men = 66 + (13.7 x weight) + (5.0 x height) – (6.7 x age)
- Women = 655 + (9.6 x weight) + (1.8 x height) – (4.7 x age)

**REE** (Resting Energy Expenditure)

- REE = 1.2 x BEE

**EE** in critical illness:

- EE should always be measured, or calculated, and then corrected depending on the concomitant

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initiation (early vs late) of PN in critically ill adults in whom caloric targets cannot be met by EN alone, especially after the publication of the results of the EPaNIC trial (Casaer et al. 2011). Casaer et al. found that there was no significant difference in mortality between late initiation and early initiation of PN among patients in the ICU who were at risk for malnutrition, despite the use of early EN plus micronutrients in a protocol that prevented hyperglycaemia. However, withholding of PN until day eight was associated with fewer ICU infections but a higher degree of acute inflammation. Late initiation of PN was also associated with a shorter duration of mechanical ventilation, a shorter course of RRT and a shorter ICU stay, despite a slight increase in hypoglycaemic episodes (Casaer et al. 2011). Unlike the EPaNIC trial, which compared semi-starvation for one week to early glucose load followed by hypercaloric low protein PN within 48 hours, Heidegger et al. started the intervention on day four to maximise the potential for EN delivery, in keeping with ESPEN guidelines (Heidegger et al. 2013). Moreover, as opposed to the EPaNIC trial, their EN group was a true control group demonstrating cumulative increasing energy deficit (indirect calorimetry): 77±25% energy target vs. 104±16% (group with supplemental PN), and their population was composed exclusively of patients with a real indication of nutritional therapy, ie failure of EN on day three.

• What Amount of Calories Should be Used in AKI?

Overfeeding should be avoided at all times, since this may result in hyperglycaemia, excess lipid deposition, azotaemia, excess carbon dioxide CO2 production with difficult weaning from the respirator and infectious complications. Although not based on solid evidence, recent recommendations suggest a non-protein energy supply of 25 to 30 kcal/kg/day in men and 20 to 25 kcal/kg/day in women (Casaer et al. 2008). The proposed proportions of non-protein energy supply are 70% to 75% of carbohydrate and 25% to 30% of fat. Recent trials have renewed interest in hypocaloric feeding, and showed that combining normal protein with reduced caloric supply (caloric intake of between 33% and 66% of the target) resulted in fewer infectious complications and reduced ICU length of stay (Casaer et al. 2011; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network 2012; Rice et al. 2011; Arabi et al. 2011. The use of indirect calorimetry is recommended.

• What Amount of Proteins Should be Given in AKI?

The goal is to improve protein synthesis and nitrogen balance. Although negative nitrogen balances are associated with the worst outcomes, there are no randomised studies comparing different protein or nitrogen intakes with regard to clinical outcomes in ICU patients. Although the ideal amount is still debated, a protein intake of between 1.2 and 1.6 g/kg/day (0.16 to 0.24 g nitrogen/kg/day) is usually recommended. Because many nonessential amino acids (NEAA) are not readily synthesised or increasingly used in critically ill patients, the combination of essential and nonessential amino acids is supposed to be superior. The optimal EAA:NEAA ratio has not yet been established, and can range from 2:1±4:1. If more than 0.4±0.5 g/kg/day are supplied, the addition of NEAA is mandatory. Composition of the amino acid mixture should be tailored to meet the specific metabolic requirements of uraemia (histidine, taurine, tyrosine).

• Should we Use Specific Nutritional Components in AKI?

Glutamine is the most abundant amino acid in the body, and is an important fuel for cells of the immune system. In stress situations, concentrations of glutamine decrease and it becomes a ‘conditionally’ essential amino acid. Although still controversial, some guidelines recommend enteral and parenteral supplementation (Fiaccadori and Cremaschi 2009). Antioxidant micronutrients (vitamins and trace elements) play a key role in metabolism, immune function, and antioxidiant processes. Because critically ill AKI patients have increased oxidative stress their antioxidant micronutrients are deficient and thus should be supplemented. Selenium, zinc,
vitamin C show promising effects on infectious complications and/or mortality in ICU patients. Recommended vitamin C in AKI varies between 30 to 100 mg but should probably not exceed 50mg/day, because inappropriate supplementation may result in secondary oxalosis. Vitamin A should probably be avoided because of the possibility of accumulation, as reported in chronic renal failure, and signs of toxicity should be carefully monitored.

Immunonutrients are nutrients with an immune-modulating effect and include glutamine, arginine, nucleotides, and omega-3 fatty acids. Arginine is a precursor of nitric oxide synthesis, and may be detrimental in critically ill patients with severe sepsis or septic shock. A systematic review aggregating the results of randomised controlled trials and meta-analysis of enteral supplementation of omega-3 fatty acids (fish oil) in patients with acute respiratory distress syndrome demonstrated that enteral formula enriched with fish oils significantly reduces mortality and ventilator days and tended to reduce ICU length of stay (Heyland and Dhaliwal 2005; Heyland et al. 2001). A role for exogenous omega-3 fatty acids in human renal protection is, at this moment, purely speculative. Cocktails of several immunonutrients and antioxidants (containing glutamine, arginine, nucleotides, and omega-3 fatty acids) in critically ill patients, however, showed no difference in clinical outcome with standard EN (Heyland et al. 2013).

- What Can we Recommend During Continuous RRT (CRRT)?

The effect of CRRT on EE and protein catabolic rate is probably small and not clinically relevant. Blood-membrane contact during RRT may induce a protein catabolic effect, but this may be of debatable nutritional significance. The exact metabolic fate of the administered amino acids is unknown. They could be used for the synthesis of ‘beneficial’ proteins or burnt for energy, but they could also join the inflammatory mediator pool (oil on the fire). The daily amino acid losses with RRT may reach between 10 and 15g (0.2 g/kg/day) especially with high flux dialysers (and this loss should be integrated by artificial nutrition). On the other hand, extracorporeal losses of lipoproteins are not to be expected. Higher amino acid intake (2.5 g/kg/day) may improve nitrogen balance in comparison with lower intake (1.2 g/kg/day), while requiring more aggressive haemofiltration. Other factors like blood pump rate and type and rate of substitution fluid may also play a role, therefore the optimal nutritional support strategy for patients with AKI requiring CRRT remains a matter of great controversy.

What about CARS?

We already mentioned the importance of comorbidities (like congestive heart failure) in the development of AKI. Within this respect, the abdominal compartment can be seen as the missing link in the pathophysiology of acute decompensated heart failure (ADHF) and worsening kidney function or cardio-renal syndrome. Indeed, increased IAP, as an extreme marker of abdominal congestion, is correlated with renal dysfunction in ADHF. Recent studies showed that raised IAP is prevalent in advanced heart failure with reduced ejection fraction and correlates with impairment of renal function (Mullens et al. 2008a). However, IAH defined as > 12 mmHg is less frequent and frank ascites is rare. Importantly, medical treatment resulting in a decrease of IAP ameliorates renal function and in cases of persistent high IAP, ultrafiltration might be beneficial (Mullens et al. 2008a, 2008b). Notably, while organ dysfunction in the intensive care literature has only been described when IAP exceeds 12 mmHg, patients with ADHF already develop worsening renal function with a much lower IAP (Mullens et al. 2008a). This might suggest that the underlying reserve of the kidneys to counteract increased IAP is limited in this setting. It is also vital to emphasise that, although the degree of renal dysfunction is probably correlated with the degree of elevated IAP, there can be a wide range of IAPs in relation to serum creatinine levels at presentation (Verbrugge et al. 2012). While we can only speculate why this discrepancy exists, it is clear that other mechanisms including coexisting systemic congestion, pre-existing renal insufficiency, as well as drugs used during the treatment of ADHF, probably play a role (Verbrugge et al. 2013). Absolute increases in blood or interstitial volume are not implied in every episode of ADHF (e.g. ‘flash’ lung oedema in diastolic heart failure). This implies that vascular redistribution is another important mechanism for elevated cardiac filling pressures. The splanchnic vasculature normally contains about 25 % of the total blood volume, a large part of which can quickly be recruited to the circulatory system through elastic recoil of the splanchnic veins and sympathetically-mediated venoconstriction (Verbrugge et al. 2012; Verbrugge et al. 2013). Because of the extensive orthosympathic innervations of abdominal capacitance veins, more blood is probably distributed to the effective circulation in states of increased sympathetic nerve system activation such as ADHF. Therefore, the term Cardio-Abdominal-Renal Syndrome (CARS) was recently coined to emphasise the potentially important role of the abdominal compartment and splanchnic vasculature in the pathophysiology of AKI and worsening chronic kidney disease in ADHF. Because fluid resuscitation may lead to fluid accumulation with second and third compartment spacing, especially in oliguric and anuric AKI, the presence of AKI carries the potential for further increase in IAP which in turn can worsen AKI itself especially if underlying morbidity like ADHF co-exists.
Conclusions

Energy needs in patients with AKI should be measured via indirect calorimetry, and should be fully covered after day four, as this will result in fewer infections, more AB-free days, shorter duration of mechanical ventilation and eventually shorter duration of RRT. In general, however, there is not enough evidence to support the effectiveness of nutritional support for AKI and further high quality randomised studies are required to provide reliable evidence of the effect and safety of nutritional support in AKI. Meanwhile, the ESPEN Guidelines should be followed, or at least clinical common sense, and we suggest using the gut if available! In non-dialysed AKI use low protein and adequate carbohydrates. For dialysed AKI patients, although no strong evidence is available, physiologic arguments favour nutritional support. If there is failure of EN, EN combined with supplemental PN should be used. If PN is to be used, commercially available all-in-one three chamber bags are convenient either for central or peripheral vein administration. Fluid accumulation should be avoided and IAP needs to be measured. In case of worsening heart and kidney function, think of CARS!

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