Module 15.1.

Acute Kidney Injury

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Learning Objectives

- To learn about nutritional issues in Acute Kidney Injury (AKI);
- To learn about the effects of AKI on nutrient and substrate metabolism;
- To learn about the impact of protein-energy wasting on clinical outcome in AKI;
- To learn about the nutritional requirements in AKI;
- To learn the goals of nutritional support in AKI;
- To learn the best approach to nutritional support in AKI.

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Key Messages

- AKI in the critically ill patient seldom occurs as isolated organ failure, and is more often a component of the multiple organ failure syndrome, occurring during severe and often prolonged catabolic phases of the critical illness, and intensified by the specific metabolic derangements associated with acute loss of kidney function;
- Patients with AKI often develop protein-energy wasting (PEW) (pre-existing and/or hospital acquired), which is itself a major negative prognostic factor; nutritional support is frequently required, in the form of parenteral and/or enteral nutrition, even though

there is no evidence from randomized controlled studies concerning its favourable effect on major outcomes;

- The primary goals of nutritional support in AKI are basically the same as those suggested for critically ill patients with normal renal function, i.e., to ensure the delivery of adequate amounts of nutrients, to prevent protein-energy wasting with its attendant metabolic complications, to promote wound healing and tissue repair, to support immune system function, and to reduce mortality;
- Patients with AKI on renal replacement therapy (RRT) should receive at least 1.5 g/kg/day of protein, indirect calorimetry should be preferred for a more precise determination of the amount of energy required and to avoid under- or overfeeding. If indirect calorimetry is not available, 20 – 30 kcal/kg/day are recommended. Lipid supply should represent at least 30-35% of calorie intake. To compensate for protein and amino acid losses during RRT, protein supply should be increased by some 0.2 g/kg/day;
- Even in patients with AKI, the enteral route represents the preferred method of nutrient delivery; however, especially in the presence of gastrointestinal dysfunction, parenteral nutrition is often required to meet nutritional requirements;
- Due to the loss of the kidney's homeostatic function, and the frequent need for renal replacement therapy, patients with AKI are especially prone to complications of nutritional support, such as hyperglycaemia, hypertrygliceridaemia, fluid retention, electrolyte and acid-base derangements;
- Since AKI comprises a highly heterogeneous group of subjects with nutrient needs which vary widely even during the clinical course of the same patient, nutritional requirements should be frequently reassessed, individualized, and carefully integrated with the RRT;
- Nutrient needs in patients with AKI can be difficult to estimate, and should be directly measured, especially in the intensive care unit setting. In fact, recent findings suggest that hidden calorie sources not routinely taken into account - e.g calories from anticoagulants and replacement solutions for renal replacement therapy - could be quantitatively relevant in these patients.

1. Introduction

Acute Kidney Injury (AKI), is a frequently observed clinical problem in ICU patients, bearing a major independent negative impact on short- and long-term outcome (2-4). AKI is characterized by the sudden and rapid (i.e. within hours to days) deterioration in kidney function that results from ischaemic and/or nephrotoxic insults causing functional or structural changes (5). Diagnosis is based on a combination of serum creatinine level and urinary output changes. Recently, a simplified definition has been introduced (2), which takes into account the relevant prognostic impact of even relatively slight increases in serum creatinine levels (6). Thus AKI is defined as abrupt reduction in kidney function with an absolute increase in serum creatinine of either ≥ 0.3 mg/dL (≥0.265 micromol/L) within 48 hours, or a percentage increase of ≥ 50% which is known or presumed to have occurred within the prior 7 days, or a reduction in urine output (≤ 0.5 ml/kg per h for > 6 hours) (2). AKI is a common complication among hospitalized patients, with an incidence of 2147-3841 per million population per year (7, 8), or 3 to 10% of subjects (9), which can rise to 10-30% in those admitted to the ICU (10). Up to 5% of patients with AKI in the ICU may require RRT (10); common indications include azotaemia, hypercatabolism, volume overload refractory to diuretic therapy, electrolyte abnormalities (in particular hyperkalaemia), uraemic complications (such as altered sensorium, pericarditis, bleeding diathesis), severe acidosis, and severe acute intoxications, etc. (10). In critically ill patients AKI seldom occurs as an isolated organ failure, and more often represents a component of the multiple organ failure syndrome, requiring appropriate nutritional intervention as part of the integrated overall treatment strategy (11). In the specific case of patients with AKI, a close integration between nutritional support and RRT is required, especially when highly efficient renal replacement therapies are used, eg continuous veno-venous haemofiltration (CVVH), or daily prolonged intermittent dialysis, e.g. sustained low-efficiency dialysis (SLED)(12, 13). Moreover, nutritional support in AKI must take into account the peculiar metabolic derangements associated with the acute uraemic state and its complications. Most of the recommendations of the present review are taken from the ESPEN guidelines on artificial nutrition in renal patients (14, 15).

2. Nutritional Status in AKI

Patients with AKI, like other patients in the ICU, are at increased risk of nutritional depletion; however, evaluation of nutritional status in these clinical conditions is difficult, as most of the commonly utilized traditional nutritional tools (body weight and body mass index, anthropometric measurements, serum protein levels etc) are often misleading, owing to the presence of acute illness, alterations in body water distribution, and external fluid balance derangements (11, 16, 17). In particular, loss of lean body mass and accelerated muscle protein catabolism are not easily evaluable at the bedside, and no clinically useful uniform and reproducible parameters are currently available, especially in the critically ill (11, 16, 17). Moreover, body weight changes cannot be used as nutritional parameters in the presence of oedema and fluid overload, making it difficult to define dry body weight; total body water is often increased, but it is underestimated by currently available equations (18). Standard definitions related to nutritional depletion in acute and chronic renal disease have been recently developed by an expert panel convened by the International Society of Renal Nutrition and Metabolism (ISRNM) (16). Instead of the non-uniform and ill-defined terminologies used in the past, the term "protein-energy wasting" (PEW) has been proposed, to indicate "a condition of

decreased body stores of protein and energy fuel stores (i.e. lean body mass and fat masses), which can occur in either AKI or CKD, regardless of the cause, and can be associated with diminished functional capacity related to metabolic stresses" (16). Since there is no single parameter allowing the diagnosis of kidney disease-related PEW, the recommendation is to use four categories of diagnostic criteria: biochemical (such as albumin, or prealbumin), body weight loss, decreased muscle mass and low energy and protein intakes (11, 16). Further studies are needed, in order to better define and validate new multidimensional criteria for nutritional status evaluation in AKI. Few data are currently available for evaluating nutritional status in AKI, although PEW seems to be a frequent problem, as shown by a prospective cohort study reporting the presence of PEW in 42% of the 309 patients whose nutritional status was evaluated on admission to the ICU by the Subjective Global Assessment (SGA), a multidimensional clinical tool based mainly on anthropometric and dietary intake evaluation (19). Skeletal muscle is the largest store of lean body mass (LBM) (about 40%) and is extremely important for numerous body functions. Moreover, the amount of remaining lean body mass (mainly represented by the skeletal muscle cell pool) when patients are discharged from the ICU makes a significant impact on whether and how patients will recover, and how much functional capacity they will regain (20). In clinical practice, imaging techniques such as DEXA, CT scan and MRI are considered gold standards to assess lean body mass. However, all of these methods are difficult to implement in the ICU on a regular basis, especially for monitoring, they may involve exposition to radiation and are expensive. Ultrasound (US) however is commonly available in many different clinical settings and is easily applicable at the bedside to different skeletal muscle groups, even in critically ill patients (21). US allows direct and serial measurements of muscle cross-sectional diameter and area, as well as the identification of muscle wasting during an ICU stay (21-24). A good correlation between US measurements of cross-sectional area, thickness and echogenicity, and muscle function and strength has been demonstrated in ICU patients (25). In addition, intra and inter-observer reliability of quadriceps femoris muscle US has been recently demonstrated in critically ill patients with AKI, with excellent repeatability even after sudden shifts in fluid distribution, such as in the case of patients on RRT (26).

Fundamentally from the clinician's point of view, despite the shortcomings of the measurements of malnutrition, a patient with a poor nutrient intake and increased catabolism is likely to be in negative energy and protein balance and therefore exposed to the impaired mental and physical function and poor outcome known to be associated with that condition, unless adequate nutritional support is given. Continued starvation is not a sensible or ethical option, which accounts for the difficulty in performing controlled trials of nutritional intervention. Many factors are likely to contribute to PEW in patients with AKI, including inadequate nutritional support, pre-existing poor nutritional status, superimposed catabolic illnesses (sepsis, trauma, surgery, chemotherapy etc.), acidosis, blood losses, etc (11) (**Table 1**). Moreover, a key role is thought to be played by specific derangements in metabolic and hormonal pathways.

3. Nutrient and Substrate Metabolism in AKI

Major metabolic and hormonal derangements are commonly observed in AKI (11, 27), due probably to the loss of the homeostatic/metabolic function of the kidneys, and to the coexistent critical illness. These processes may have a relevant impact on nutritional support: AKI in fact is associated with alterations of water, electrolyte and acid-base metabolism, and also with specific changes in protein, carbohydrate and lipid

metabolism, combining to cause a general disruption of the "internal milieu". Metabolic changes in critically ill patients with AKI include hyperglycaemia and insulin resistance, proteolysis of skeletal muscle proteins with increased amino acid turnover and negative nitrogen balance, and altered lipid metabolism.

3.1. Glucose

Derangements in glucose metabolism are frequently observed in patients with AKI. They can complicate the use of artificial nutrition and jeopardize the patient's outcome. Hyperglycaemia in critically ill patients is associated with AKI, and prevention of hyperglycaemia in critical illness appears to be renoprotective (28). However, the initially encouraging results on the possible positive effects of glycaemic control – and in particular of the so-called tight glycaemic control – in the prevention of AKI and the need for RRT (29-32), have not been confirmed in a recent meta-analysis based on seven RCTs with 11,425 patients (33). Thus, the overall results of currently available studies do not support target values as low as 80–110 mg/dl either in critically ill patients in general, or in those with AKI. As the optimal glycaemic target for renoprotection in critical illness remains to be formally defined, in the case of AKI a 110–150 mg/dl range has been prudentially suggested in the 2012 KDIGO Guidelines on AKI (2). The negative effects of hyperglycaemia may be mediated by any one or any combination of the following mechanisms (27): (i) direct toxic effects of glucose overload on cells where glucose uptake is independent of insulin, such as the endothelial, epithelial, immune, and central and peripheral nervous system cells; (ii) increased generation of reactive oxygen species (ROS) and nitrogen species (peroxynitrites); (iii) activation of the inflammatory cascade (34). Moreover, hyperglycaemia negatively affects all major components of innate immunity, impairing the organism's ability to resist infection (35), and is associated with hypercoagulability, through the activation of the tissue factor pathway (36). Mechanisms of critical illness-acquired hyperglycaemia include impairment of insulin-mediated glucose uptake in skeletal muscle, and failure of insulin to suppress hepatic gluconeogenesis (37); this latter effect is due to increased release of counter-regulatory hormones, including glucagon, epinephrine, cortisol and growth hormone, leading to increased gluconeogenesis and insulin resistance. Many components of acute illness may also contribute to the hyperglycaemic state, such as the release of proinflammatory cytokines during inflammation and sepsis, and the therapeutic use of glucocorticoids and adrenergic agents. Finally, nutritional support containing excess glucose may promote further elevations in blood glucose. However, the potentially adverse effects of artificial nutrition-related hyperglycaemia, though suggested by observational studies (38, 39), still awaits confirmation by RCTs comparing patients receiving nutritional support with and without adequate glycaemic control. Since the kidneys are an important site of gluconeogenesis and insulin catabolism, they play an important role in glucose homeostasis (40). It comes as no surprise, therefore, that the loss of this homeostatic function may further aggravate the metabolic changes produced by critical illness, with its inflammation, increased oxidative stress, and worsening insulin resistance. In experimental models of AKI, acute loss of renal function is associated with accumulation of oxidation and nitration free products in the plasma (41). Patients with AKI also show an altered balance between pro- and anti-inflammatory responses, with raised levels of both pro- and anti-inflammatory cytokines, which is independent of the presence of sepsis. These changes are significantly associated with an increased risk of death (42). Finally, oxidative stress-related gene polymorphisms, associated with higher levels of nitrogen oxidative species, also predict an adverse outcome (43).

3.2. Protein

Experimental models suggest that protein metabolism is altered in uncomplicated AKI (44). Acute uraemia following bilateral nephrectomy in rats is associated with a significant increase in catabolic activity (45); studies in other models of acute uraemia have documented the occurrence of an early increase in protein degradation/release from skeletal muscle, along with depressed protein synthesis (46-48); finally, another study showed alterations in the transport and intracellular concentrations of amino acids in the skeletal muscle of rats with AKI (49). As happens in other catabolic conditions, skeletal muscles are the main source of amino acids as gluconeogenic precursors; amino acid extraction from plasma, hepatic gluconeogenesis and urea production are increased, while the synthesis of protein, apart from visceral and acute phase proteins, is inhibited (11, 27). Urea synthesis is upregulated in experimental AKI, probably as a result of changes in gene expression (50); these changes may play an important role in the pathogenesis of protein catabolism and the negative nitrogen balance characteristic of this syndrome. Turning our attention to the clinical setting, there is no clearcut demonstration that AKI is inevitably associated with a catabolic status. Acute uraemia seldom occurs as an isolated event in the ICU, and the protein catabolic state of the critically ill patients with AKI is most frequently multifactorial. Many non-specific mechanisms, associated with the underlying stress response to critical illness and its complications are involved (trauma, sepsis, complicated surgery, etc.), as well as the specific effects of renal failure and its treatment (**Table 1**) (11).

Table 1
Factors involved in the pathogenesis of protein catabolism in AKI

Inadequate supply of nutrients
Uraemic toxins (?)
Endocrine factors
Defective response to insulin (insulin resistance)
Increased secretion of catabolic hormones (glucagon, catecholamines, glucocorticoids etc.)
Resistance to and/or decreased/suppressed secretion of growth/anabolic factors
Critical illness/Acute phase reaction/Systemic Inflammatory Response (cytokines)
Metabolic acidosis
Proteases (ubiquitine-proteasome system etc.)
Loss of nutritional substrates by renal replacement therapy
Drug effects

Whatever the contributory causes are, ICU-acquired AKI results in increased protein catabolism with negative nitrogen balance, loss of lean body mass with skeletal muscle wasting, and enhanced production of urea nitrogen; in most cases this catabolic state cannot be reduced by feeding, although this does counteract the starvation element and therefore reduces the net rate of body tissue loss (27).
Another important factor in the loss of lean mass in ICU patients is immobilization, causing muscle wasting that can only be reversed by physical activity. The extent and the severity of protein catabolism can be evaluated by measuring the excess urea appearance above nitrogen intake (27): values of 5-10 g/day indicate moderate catabolism, > 10 g/day severe catabolism. There is evidence that, in human AKI, the amino acid pool balance is altered, in both its plasma and intracellular compartments, with enhanced elimination of most amino acids from plasma and impaired tissue utilization of exogenously infused amino acids; amino acid oxidation is stimulated, but

amino acid transport into muscle is impaired. Finally, several non-essential amino acids (e.g. tyrosine) become conditionally essential (27, 51).

3.3. Lipids

There are several derangements of lipid metabolism in patients with AKI. Plasma levels of triglycerides and very low-density lipoprotein (VLDL) levels are increased, while those of total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) are decreased (52). Impaired lipolysis is the most important cause of plasma lipid changes in AKI (53), the activity of both peripheral lipoprotein lipase and hepatic triglyceride lipase being reduced by about 50% (52-54); moreover, lipoprotein lipase activity is inhibited if acidosis coexists (55). Fat clearance following parenteral administration of lipids is reduced in AKI. Metabolism of commercially available fat emulsions is similar to that of endogenous VLDL; thus, in AKI clearance of lipid emulsions is slowed, especially when the administration rate is high (52). In spite of the reduced rate of clearance of exogenous lipid particles from plasma, fatty acid oxidation is preserved in AKI, and lipids are a key energy substrate in AKI, as suggested by the low respiratory quotient measured in this clinical setting (56).

4. Nutrient Requirements in AKI

4.1. Macronutrients

In general, the nutritional requirements of patients with AKI depend more on the severity of the underlying disease, pre-existing nutritional status, and acute/chronic comorbidities, than on the AKI itself (14, 15). RRT also has an important influence through loss of amino acids during dialysis. It is commonly accepted that, even in multiple organ failure, energy expenditure of critically ill patients rarely amounts to more than 130% of predicted energy expenditure (57), and is influenced by the severity but not the type of acute illness (trauma, medical disease, major surgery etc.) (58). Also in patients with ICU-acquired AKI no major modifications of energy metabolism can be attributed to the syndrome *per se*, energy expenditure usually depending on the coexistence of critical illness and its complications (59). Faisy et al. could not find, in mechanically ventilated ICU patients, any changes in resting energy expenditure due to AKI (60). Indirect calorimetry (IC), a non-invasive method that allows exact assessment of resting energy expenditure (REE) based on individual oxygen consumption and carbon dioxide production in the exhaled air (61), currently represents the gold standard for measuring energy needs. These measurements can be used in order to define expected energy expenditure and to guide the administration of energy support in individual ICU patients, avoiding both underfeeding and overfeeding, two conditions very commonly observed in the ICU (62-67). Unfortunately, IC is scarcely used in clinical practice, due to limited availability and costs. When energy needs are not measured, the use of validated equations to estimate REE may often lead to under- or overestimation of energy needs (66-70). Specific situations such as use of sedatives, mechanical ventilation, multiple organ failure and fluid balance derangements (fluid overload or volume depletion) leading to major changes in body weight may increase the risk of over- or underfeeding when clinicians use currently available equations, especially if the basal metabolic rate is corrected by predefined stress correction factors (67, 70).
The optimal protein intake of AKI patients has not so far been defined; however, studies have documented that the protein catabolic rate (PCR) in AKI patients on artificial

nutrition (PN or EN or a combination of both regimens) varies from 1.4 to 1.8 g/kg/day (71-75). By and large, to achieve less negative or nearly positive nitrogen balance, patients with AKI requires an intake of at least 0.25 g of nitrogen/kg/day which corresponds closely to the above PCR values. Few data are currently available on the effects of very high protein intakes on nitrogen balance in AKI patients. When nutrient intakes were set at 2.5 g/kg/day of protein and 35 kcal/kg/day of energy, only one third of patients achieved a positive nitrogen balance (75). In a cross-over study in AKI patients receiving an isocaloric regimen - in most cases through EN - nitrogen balance was positively related to protein intake, with a positive nitrogen balance being more likely to be obtained with intakes larger than 2 g/kg/day (0.3gN/kg/d) (76). However, no data on this topic are currently available from RCTs, and evidence concerning advantages of very high protein intakes in critically ill patients with AKI is lacking. Finally, it is to be emphasised that, in many patients with AKI, hypercatabolism cannot simply be overcome by increasing protein or amino acid intake much above 0.25-0.3 g nitrogen/kg/day, even when energy intake is optimal. Above this level of nitrogen intake any further increase is simply catabolised to urea and contributes nothing to protein synthesis, although an increase may be required to compensate for losses during dialysis. A higher provision of essential amino acids (EAA), does not appear to be advantageous in this clinical setting, and both EAA and non-essential amino acids (NEAA) are recommended in AKI (14, 15). No data are currently available for other particular amino acids, e.g. glutamine. Safety issues concerning the administration of very high amino acid loads in AKI need to be considered, even when highly efficient daily RRT modalities are used (CRRT or SLED). Nutritional support is able to significantly increase amino acid levels in AKI patients (77), but no data are currently available about the possible toxic/protective effects of amino acids in this clinical setting (78). Thus, before recommending higher intakes of amino acids/proteins than previously suggested, we need more data. The optimal energy to nitrogen ratio has not been clearly defined in AKI patients, although, in an observational study of patients on CRRT, less negative or weakly positive nitrogen balance values were predicted by linear regression analysis models when protein intakes of 1.5 g/kgBW/day were provided in parallel with non-protein energy intakes of about 25 kcal/kg BW/day; simply increasing the calorie to nitrogen ratio in this study was not invariably associated with better nitrogen balance (79). With a protein intake of 1.5 g/kg/day, an increase in energy provision up to 40 kcal/g/day did not improve nitrogen balance compared with lower energy intakes (30 kcal/kg/day); instead, more severe metabolic complications (hypertriglyceridaemia, hyperglycaemia) ensued (80). In conclusion, AKI patients on RRT should receive at least 1.5 g/kg/day of protein (= 0.25g N/kg/d), and energy needs should be measured by IC. However, if IC is not available 20-30 kcal/kg/day should be prescribed according to recent guidelines (2, 14, 15, 81). In this setting, the protein intake should be increased by about 0.2 g/kg/day to compensate for protein and amino acid losses during RRT, especially when high-flux filters and CRRT are used. The losses can be quantified as about 0.2 g amino acids/l of ultrafiltrate (up to 10–15 g amino acids per day), and 5 g-10 g/day of protein (14, 15). For relatively 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) (27). Lipids should represent about 30-35% of total non-protein energy supply. In the case of parenteral nutrition this can be administered to the patient by giving 0.8-1.2 g/kg/day of lipid from 10-30% lipid emulsions, or as a part of commercially available three-in-one total nutrient admixtures.

Lipids should be infused over 18-24 hours, and serum triglycerides should be monitored, stopping lipid administration when triglycerides exceed 400 mg/dL (~5.3 mmol/L). Even though the use of parenteral MCTs may theoretically result in lower serum triglycerides because of their faster oxidation, pharmacokinetic studies have failed to show any clear advantages, in terms of plasma clearance of triglyceride, of mixed MCT/LCT lipid formulas compared to LCT-only emulsions. However, in a short-term cross-over study in patients with AKI on RRT and total parenteral nutrition, MCT/LCT emulsions yielded lower serum triglyceride levels than the LCT formulas (80). Lipid losses through the filters do not occur during haemodialysis or haemofiltration.

4.2. Micronutrients

Micronutrient requirements (trace elements and vitamins) have been poorly investigated in patients with AKI, in whom levels of trace elements, (essential nutrients with regulatory, immunological and antioxidant functions), can be lower than normal (11, 81-83). However these alterations, rather than being a specific consequence of AKI, are likely to be the product of widely different factors (27): acute phase reaction/critical illness, leading to variable protein binding, redistribution of elements between plasma and tissues, acute losses of biological fluids, dilution, varying concentrations of trace elements in dialysis/haemofiltration fluids, effects of enteral or parenteral nutrition fluid, and analytical problems, etc. Moreover, RRT fluids (dialysis fluid or sterile solutions for fluid replacement in the case of haemofiltration) may have variable content of trace elements, at concentrations often difficult to detect; finally, the effects of RRT on the removal of mainly protein-bound trace elements are far from clearly defined.
Data from *in vitro* studies indicate that selenium, chromium, copper and zinc can be removed from plasma by convective/diffusive RRTs (84). In the clinical setting CVVH is associated with reduced plasma selenium and zinc but high chromium levels; there was little loss of the former two elements in the ultrafiltrate, whereas considerable losses of chromium and copper were observed (81). Zinc was detected in effluent fluid in CVVHDF, but zinc balance was nonetheless positive, owing to the zinc content of PN and replacement fluid solutions, and its presence as a contaminant of the anticoagulant solution (trisodium citrate). The combination of these sources thus exceeded the losses due to CRRT (83, 85). In contrast, the association of convection and diffusion in CVVHDF was associated with selenium losses (85), regardless of the buffer solution used, resulting in a daily negative balance equivalent to twice the daily intake from standard formula parenteral nutrition fluids (83). In ICU patients with AKI, plasma levels of water-soluble vitamins, such as vitamin C (81), thiamine, and folic acid, may be lower than normal (86), due mainly to the losses occurring through the extracorporeal circuit. In CVVH vitamin C losses can reach up to 600 µmol/day i.e. 100 mg/day, and folate losses up to 600 nmol/day (84, 86); in CVVHDF thiamine losses may exceed 1.5 times the daily provision of the vitamin from standard total parenteral nutrition solutions (83). In experimental AKI, plasma retinol levels are increased, whereas, in patients with AKI, serum levels of vitamin A and vitamin E are decreased (14, 15, 27); activation of vitamin D3 is impaired in AKI. Vitamin C administration should not usually exceed 50-100 mg/day, since inappropriate supplementation may lead to secondary oxalosis; higher intakes (up to 150-200 mg) may be needed when continuous modalities of RRT are used. No supplementation of fat soluble vitamins is usually necessary in AKI. Derangements in fluid, electrolyte and acid-base equilibrium, such as hypo- and hypernatraemia, hyperkalaemia, hyperphosphataemia, metabolic acidosis, etc. commonly occur in critically ill patients with AKI (8, 9). Intensive (daily) RRT can readily correct these

abnormalities by appropriate regulation of the composition of the haemodialysis/haemofiltration fluids and on the intensity of RRT.

5. Goals of Nutritional Support in AKI

The primary goals of nutritional support in AKI, do not substantially differ from those applying to other catabolic critically ill patients: i.e. to ensure the delivery of energy and protein in such amounts as to prevent protein-energy wasting, to preserve lean body mass and nutritional status, to avoid further metabolic derangements and complications, to improve wound healing, to support immune function, and to reduce mortality. In the specific case of AKI, it is recommended that nutritional goals also include attenuation of inflammation and improvement in antioxidant activity and endothelial function (11). Finally it should be remembered that a positive nitrogen balance with gain in lean mass is impossible in a catabolic and relatively immobile patient. All that can be achieved by nutritional support is to slow the rate of muscle wasting and to preserve as much lean mass as possible. Regain of lean mass with positive nitrogen balance must await convalescence when catabolic stimuli have resolved and a combination of food and physical activity can stimulate muscle to regenerate.

6. Protein Energy Wasting, Nutritional Support and Outcome in AKI

Nutritional status is a major prognostic factor in the patient with AKI. Severe PEW, as defined by SGA (19), impairs outcome, whether defined by the length of hospital stay, complication rates, or mortality rates; in the same study severe malnutrition was predictive of in-hospital mortality independently of the other well-known complications and co-morbidities of AKI. Even though it would appear logical to start aggressive nutritional support early in AKI, especially in highly catabolic patients, the benefits of such an approach on morbidity and mortality remain unproven and controversial. This is due to the heterogeneity/complexity of the syndrome, and to major methodological flaws in the available studies. Further studies are therefore required before firm recommendations can be made concerning the timing of nutritional support. Most published studies of the effect of nutritional support on outcome in AKI involve the use of the parenteral route. Four studies published during the ’80s analyzed the effect of parenteral nutrition on mortality. In one retrospective study (87), parenteral nutrition was associated with better outcome, while in the other three prospective studies (88-90) no survival advantage was demonstrated. However, such studies were methodologically flawed due to suboptimal selection of patients, population heterogeneity, lack of stratification for severity of illness, nutritional status, RRT dose received, use of historical controls, quantitative and qualitative inadequacy of caloric and nitrogen intake, etc. In a prospective randomized trial assessing calorie and protein needs of critically ill anuric patients requiring CRRT, nitrogen balance was positively related to protein intake and more likely to be attained with protein intakes of more than 2 g/kg/day (76). Similar data were obtained in a group of patients with milder forms of non-oliguric AKI (91). A negative nitrogen balance was directly associated with worse ICU and hospital outcomes (76) in AKI patients receiving mixed nutritional support (enteral plus parenteral); in the same study the use of the enteral route had a statistically significant advantage in terms of outcome. Enteral nutrition was also associated with a positive outcome when regression analysis methods were applied to a large observational cohort of AKI patients in the ICU (4). There is sparse and indirect evidence suggesting that amino acids might favour the recovery of renal function. Intravenously or enterally administered amino acids increase renal plasma flow and glomerular filtration rate in animals and in normal subjects (92, 93), and GFR can improve moderately following an amino acid load in chronic renal failure (94, 95) and in cirrhotic patients (96). However the information available on the possible beneficial effects of amino acids in patients with AKI is scarce.

In one experimental study enteral nutrition was superior to parenteral in this respect (97). Positive effects of a high amino acid parenteral regimen on renal function in terms of diuresis preservation and water balance have recently been suggested in patients with non-oliguric forms of AKI (91).

7. Indications for Nutritional Support and Route of Feeding in AKI

The indications for nutritional support in AKI are the same as those in other critically ill patients (57). By the same token, the route of feeding depends more on GI function than on the presence of AKI. In the past, AKI patients were mostly fed via the parenteral route, but in recent years we have seen a trend towards the enteral route becoming the first choice for nutritional support. Parenteral nutrition is indicated in AKI when the GI tract cannot be used, or when EN appears inadequate to reach nutrient intake goals (98). Renal failure can impair gastrointestinal motility (16). Apart from AKI itself, other factors present in critically ill patients are known to impair GI function, e.g. medications such as sedatives, opiates, or catecholamines; hyperglycaemia; electrolyte disorders; mechanical ventilation etc. Finally, AKI is a well-defined risk factor for upper -gastrointestinal bleeding (98), and it is uncertain whether enteral nutrition has any protective effects on this risk. Data on enteral nutrition in AKI are scanty. The safety and efficacy of nutritional support administered solely via nasogastric tubes was evaluated in an observational study on 182 patients with AKI, receiving either a standard formula or a disease-specific formula for patients with renal failure on haemodialysis (99). No evidence was found that AKI is associated with a consistent increase of gastrointestinal, mechanical, or metabolic complications during enteral nutrition. High gastric residual volumes were more frequent in patients with AKI compared to those with normal renal function, but in general the enteral route was safe and effective (99). Underdelivery of targeted energy intakes due to enteral nutrition-related complications was a minor problem; however, with use of the enteral formulae currently available on the market, it may be difficult to achieve the protein intake usually recommended in AKI patients. Parenteral amino acid supplementation can therefore be required, especially in patients with AKI on renal replacement therapy (14, 15). In one study of patients with AKI in the ICU the combination of enteral and parenteral feeding allowed successful nutritional support in most cases, since patients received 99% of calculated needs and 89% of measured energy expenditure (76). Thus the two routes of nutritional support are to be considered complementary and not mutually exclusive. For short time periods, peripheral PN can be used in AKI patients, according to fluid restriction needs and calorie/protein goals. However, due to the need for fluid restriction and the high osmolarity of more concentrated, commercial three-in-one admixtures, parenteral nutrition in AKI patients, especially those in the ICU, must generally be infused via a central vein (14, 15).

8. Disease Specific Formulas for Nutritional Support in AKI

Although standard enteral formulae are adequate for the majority of critically ill patients with AKI, there may be a case for using the disease specific formulae that were designed for patients with chronic renal failure with their high energy (1.8 - 2 kcal/ml) and protein (70 - 81 g/l) and low electrolyte content (99). The difficulty in developing a disease-specific formula for AKI patients is related to the wide variation in metabolic changes and the differing individual requirements. However, even with the most suitable disease-specific enteral formulae, parenteral supplementation of amino acids is likely to be required in order to meet the targeted nitrogen requirement (99). For parenteral

nutrition, standard formulae (both amino acid solutions and commercial three-in-one nutrient admixtures) containing both essential and non-essential amino acids can be employed. In some patients, the three-in-one nutrient admixtures without electrolytes (i.e. without sodium, potassium etc.), which are now commercially available, can be used with caution and careful monitoring, and/or customized according to patient needs. Whether immune enhancing diets should be given to AKI patients remains an unsettled question.

9. Specific Problems of Nutritional Support in AKI Patients on RRT

Issues concerning specific aspects of nutritional support in patients with AKI on RRT have recently revolved around the possible hidden calories in solutions utilized during RRT, and the risk of hypophosphataemia linked to the efficient removal of phosphorus by RRT itself.

Citrate has progressively emerged as a safe and efficacious alternative to heparin for the anticoagulation of the extracorporeal circulation during RRT (100, 101). Citrate is partially removed from the blood by the RRT itself, and the citrate load for the patient depends on the balance between the total citrate dose administered in the circuit and mass removal by RRT. Citrate escaping the circuit remains in the systemic circulation of the patient and is metabolized in the liver, the renal cortex and in skeletal muscle. Because citrate is a tricarboxylic acid intermediate of the Krebs cycle in the mitochondria, it does not need insulin to enter the cells and to be utilized as energy substrate (100). In the case of standard modalities of continuous RRT with trisodium citrate solution, it can be estimated that about 300-500 millimoles of citrate may reach the patient's circulation every day, providing 100-200 kcal/day (102, 103). In other protocols for continuous or prolonged intermittent modalities of RRT, that are based on the use of ACD-A (acid-citrate-dextrose) as anticoagulant (a solution containing sodium citrate, citric acid and 2.5% dextrose), and with lactate as a buffer, the estimated daily caloric load from citrate, glucose and lactate can be as high as 1200 kcal/day (102, 103). This potentially excess energy intake provided by RRT might be partially prevented by using low citrate protocols (101), bicarbonate buffer solution for replacement, citrate solutions other than ACD at lower doses and without glucose (102, 103), or by the utilization of prolonged intermittent modalities of RRT, such as SLED. Moreover, the contribution to the total calorie count by additional calories given in the form of citrate, lactate, and glucose from dialysis/haemofiltration solutions must be included in the cumulative energy balance of the patient.

The incidence of hypophosphataemia is high among ICU patients, and it can be further increased by the use of prolonged and intensive modalities of RRT that achieve a very efficient clearance of phosphate (104). Severe hypophosphataemia has been associated with respiratory muscle weakness (105, 106), ventilatory failure, myocardial dysfunction and encephalopathy in critically ill patients (105); moreover, a higher incidence of prolonged respiratory failure requiring tracheostomy has been documented in patients with AKI on continuous RRT (107). To reduce the incidence of hypophosphataemia, and the need for *ad hoc* intravenous treatment (usually a parenteral phosphorus supplementation of at least 20-30 mmol/day is required), phosphate can be added to replacement and/or dialysate solutions (108-110). Chemico-physical incompatibility and calcium–phosphate precipitation are not a concern when regional citrate anticoagulation is used along with calcium-free dialysate/replacement solutions; the use of a calcium and phosphate-containing replacement solution in the form of a more concentrated citrate solution in combination with a new phosphate-containing replacement fluid (phosphate

1.2 mmol/L) and a standard bicarbonate concentration (30 mmol/L) appear to be effective in preventing hypophosphataemia during CRRT with citrate, allowing the avoidance of intravenous phosphate supplementation (111, 112).

10. Summary and Decision Tree for Nutritional Support in AKI

Patients who develop AKI often have pre-existing or hospital acquired protein-energy malnutrition, which is a major negative prognostic factor in this clinical condition. Despite the lack of evidence from controlled trials of its effect on outcome, nutritional support by the enteral or parenteral route appears clinically indicated in most cases of ICU-acquired AKI to prevent deterioration in nutritional state with all its known complications. Extrapolating from data in other conditions, it seems intrinsically unlikely that starvation of a catabolic patient is more beneficial than appropriate nutritional support by an expert team with the skills to avoid the potential complications of EN and PN. By the same token it is ethically impossible to conduct a trial in which the control group undergoes prolonged starvation. The primary goals of nutritional support in AKI are the same as those for critically ill patients with normal renal function, i.e., to ensure the delivery of adequate nutrition, to prevent protein-energy wasting with its attendant metabolic complications, to promote wound healing and tissue repair, to support immune system function, to accelerate recovery, and to reduce mortality. Patients with AKI on RRT should receive a basic intake of at least 1.5 g/kg/day of protein with an additional 0.2 g/kg/day to compensate for protein lost during RRT. Energy needs should be preferably measured by indirect calorimetry, however, in the absence of this technique, energy intake should consist of 20-30 kcal/kg/day with at least 30-35% from lipid. For nutritional support, the enteral route is preferred, although it often needs to be supplemented by the parenteral route in order to meet nutritional requirements. On the basis of recommendations made in recent guidelines on the topic (14-15), a decision tree for nutritional support in AKI patients with established protein-energy wasting or who are at risk of developing it has been proposed (**Fig. 1**)**.**

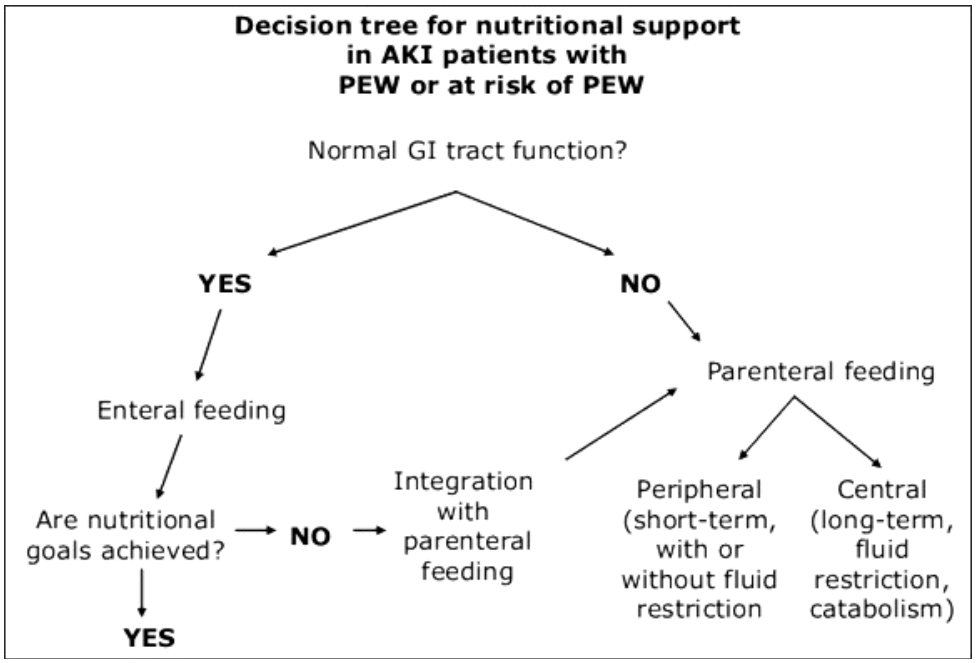

Fig. 1 Decision tree for nutritional support in AKI patients with PEW or at risk of PEW

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