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Nutrition support therapy in acute kidney injury: Distinguishing dogma from good practice

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Abstract

Acute kidney injury (AKI) is a frequently observed complication in critically ill patients. Its presentation may range from the early risk of renal dysfunction to complete renal failure. Morbidity and mortality in the AKI patient increase with the decline of renal function. Appropriate nutrition therapy is essential in the medical management of the AKI patient. Assessment of nutritional requirements should take into account the patient's underlying complication, comorbid medical conditions, and severity of the renal dysfunction. Various stages of AKI determine the direction of nutrition therapy. Additionally, understanding the macro- and micronutrient modifications and electrolyte and vitamin alterations that should be implemented are vital for better patient outcomes.

Introduction

Acute kidney injury (AKI) is a frequent complication in hospitalized patients. The incidence of AKI and AKI with renal replacement therapy (RRT) is about 2000 to 3000 and 200 to 300 per million population per year, respectively. Morbidity and mortality are increased in AKI patients, with a mortality rate of 50% to 60% in patients with AKI receiving RRT [1]. Associated AKI malnutrition further increases the risk of complications; therefore, nutrition therapy is a mainstay for AKI treatment. Appropriate, adequate nutrition must be implemented to suppress resulting hypermetabolism and hypercatabolism.

AKI Classification

In the past, "acute renal failure" was defined in a multitude of ways based on differing clinical and laboratory features. Failure to define and classify the various stages of acute renal failure led the Acute Dialysis Quality Initiative (ADQI) group to collaborate, define, and identify a staging and outcomes system for acute renal failure [2,3]. Foremost, the term "acute renal failure" was replaced by "acute kidney injury," a more encompassing term. The ADQI consensus definition of AKI is denoted by the acronym RIFLE, which refers to three stages of increasing severity classes —*risk*, *injury*, and *failure*—and two outcome classes—*loss* and *end-stage renal disease*. The three severity classes are based on combined criteria of serum creatinine concentration or glomerular filtration rate and urine output, with the worst of each criterion used. The two clinical outcome criteria—loss and end-stage kidney disease—are based on the relation to duration of loss of kidney function [2,3].

Although the RIFLE criteria took the first step toward defining and classifying AKI, emerging data imply that smaller changes in serum creatinine than those initially considered might be associated with adverse outcomes; subsequently, the Acute Kidney Injury Network modified the RIFLE criteria so that patients meeting the definition for AKI could be diagnosed and staged [4••]. The proposed staging system retains the emphasis on acute alterations in serum creatinine and/or urine output.

According to the Acute Kidney Injury Network [4••], diagnostic criteria for AKI include an abrupt (within 48 hours) reduction in kidney function, currently defined as an absolute increase in serum creatinine ≥ 0.3 mg/dL (≥ 26.4 μmol/L), a percentage increase in serum creatinine ≥ 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria < 0.5 mL/kg per hour for > 6 hours). Three stages for AKI were implemented based on the modified RIFLE criteria (Table 1) [4••].

Nutrition Assessment in AKI

Malnutrition is an independent risk factor for hospital mortality and is common in patients with AKI. Anorexia, impaired protein metabolism and transport, oxidative stress, metabolic acidosis, nutrient losses through the hemodiafilter, and patient comorbidities are contributing factors to malnutrition [5]. Additionally, hypermetabolism and hypercatabolism are common because AKI is a complication resulting from surgery, trauma, thermal injury, multiorgan failure (MOF), and sepsis. Proper nutrition aimed at minimizing these effects is imperative [5,6].

Nutritional evaluation of a patient with AKI includes physical assessment, anthropometric measurements, and laboratory values. However, because of the disease process, the patient's resulting edema may alter anthropometric measurements, and fluid retention and declining renal function may potentially result in erroneous visceral protein markers (eg, albumin, prealbumin). Body weight before the onset of illness usually is a better representation of the patient's "true" weight than their actual body weight. Weight gains of 0.5 to 1 kg/d usually represent fluid retention and must not be used when determining caloric/protein nutritional goals and modifications [7].

The futility of albumin and prealbumin as markers to identify malnutrition and nutrition response in AKI has led investigators to identify an alternative marker. Insulin growth factor has been investigated and successfully used to assess a renal patient's response to nutritional support as well as a specific marker for malnutrition in patients undergoing hemodialysis. However, because information is limited, further research is necessary before insulin growth factor can be recommended for routine use [7].

Also used to assess protein breakdown in the AKI patient are nitrogen balance (measurement of nitrogen intake minus nitrogen output), urea nitrogen appearance (UNA; measurement of the net rate of protein catabolism), and protein catabolic rate (PCR; measurement of net protein degradation). For an accurate determination, the standard method for measuring a patient's

Table 1. Staging system for acute kidney injury

AKI Stage	RIFLE classification	Serum creatinine	Urine output
1	R	Increase in serum creatinine ≥ 0.3 mg/dL or increase to ≥ 150%-200% (1.5- to 2-fold) from baseline	< 0.5 mL/kg per hour for > 6 h
2	I	Increase in serum creatinine to > 200%-300% (> 2- to 3-fold) from baseline	< 0.5 mL/kg per hour for > 12 h
3	F	Increase in serum creatinine to > 300% (> 3-fold) from baseline or serum creatinine ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL	< 0.3 mL/kg per hour for 24 h or anuria for 12 h

AKI - acute kidney injury; RIFLE - risk, injury, failure, loss, end-stage renal disease.
(*Data from* Mehta et al. [4••].)

Table 2. Urea nitrogen appearance and protein catabolic rate calculations*

UNA, *g/d* = UUN + [(BUN2 - BUN1) × 0.6 × BW1] + [(BW2 - BW1) × BUN2]

Where: Net protein breakdown = UNA × 6.25; UUN = urinary urea nitrogen, *g/d*; BUN1 = initial collection of blood urea nitrogen, postdialysis, *g/L*; BUN2 = final collection of blood urea nitrogen, predialysis, *g/L*; BW1 = postdialysis weight, *kg*; BW2 = predialysis weight, *kg*.

PCR, *g/d* = UNA × 6.25

*Protein intake fluctuations and varying catabolic presentations may result in the calculation of erroneous results.
BUN - blood urea nitrogen; BW - body weight; PCR - protein catabolic rate; UNA - urea nitrogen appearance; UUN - urinary urea nitrogen

nitrogen balance requires a creatinine clearance of more than 50 mL/min/1.73 m^2, which makes utilizing the nitrogen balance in patients with AKI difficult. In patients with AKI, ascertaining the UNA is less laborious and more accurate. Table 2 describes UNA and PCR calculation [8,9].

Nutrition Support Therapy

AKI stage 1

Stage 1 AKI is associated with pre- or postrenal injury. Identification of fluid status and protein delivery is necessary. Inadequate hydration may be corrected by fluid replacement and/or appropriate modification of diuretic therapy. Azotemia resulting from overzealous protein delivery may be remedied by decreasing the provision of protein. Prerenal injury resulting from

excess volume may require sodium and fluid restriction while monitoring diuretic response. Obstruction resulting in postrenal injury requires correction of the obstruction.

Nutritional energy and protein requirements in stage 1 AKI are based on the patient's underlying disease state or complication. Stage 1 AKI has a limited effect on energy expenditure. Likewise, the provision of electrolytes, vitamins, minerals, and trace elements is based on the patient's presentation and accompanying complications.

AKI stage 2

In stage 2 AKI, the focus is on avoiding exacerbation of the kidney injury and, usually, on correcting a state of either volume depletion or excess. The need for nutrition support therapy varies in stage 2 AKI and, when necessary, can have a therapeutic and/or supportive role. Significant blood loss, diuretic abuse, prolonged vomiting, diarrhea, lack of access to adequate hydration, and abdominal vascular surgery can lead to renal hypoperfusion, requiring aggressive resuscitation. Abdominal vascular surgery requiring a prolonged ischemia time is also notorious for causing AKI, especially in patients with preexisting chronic kidney disease (CKD).

Once intravascular volume is restored, adequate urine output should return. The response to resuscitation is usually prompt, making restrictions to nutrition support unnecessary. If urine output lingers at less than 1 L/d, potassium intake may need to be limited and potassium replacement protocols discontinued.

Decreased cardiac output or hepatic failure can lead to poor renal perfusion and hypervolemia with AKI. Fluid and sodium restriction are the mainstays of therapy with aggressive diuresis. Ascites is common, contributing to early satiety and delayed gastric emptying, which can compromise oral intake. Bowel edema can interfere with nutrient absorption. The use of a continuous dobutamine infusion may cause nausea and loss of appetite. Achieving adequate nutrition support may involve postpyloric enteral feeding with a volume-controlled formula until renal function improves and hypervolemia is corrected.

In an attempt to control uremic waste accumulation, protein has been limited to 0.6 to 0.8 g/kg in AKI patients without RRT; however, this causes a risk for protein malnutrition, especially in patients who are recently postoperative and/or with other comorbidities. According to Bellomo [10], the first principle for nutrition support in renal failure states that the presence of renal failure should never lead to restrictions in nutrition support. Therefore, a patient with AKI should either be able to receive an adequate protein intake without experiencing significant azotemia or progress to RRT so that adequate nutrition can be provided and azotemia controlled. Nutrition support therapy in AKI should not focus on restricting protein to avoid RRT. A protein intake of 1.0 g/kg or greater is indicated and supportive in AKI stage 2.

Past practice in nutrition support recommended that patients with AKI be fed energy intakes up to 50 kcal/kg [11]. A high energy intake was purported to spare protein, control the buildup of nitrogenous wastes, and thus avoid the need for RRT. For nonoliguric stage 2 AKI, energy intake

in the range of 25 to 35 kcal/kg is acceptable, similar to other mildly stressed hospitalized patients.

AKI stage 3

Once AKI has reached stage 3 and RRT is necessary, nutrition support is both supportive and therapeutic. Protein and micronutrient losses occur with RRT and can be corrected by the nutrition support prescription. Hemodynamic stability dictates the RRT modality. The critically ill patient often requires continuous RRT (CRRT) initially; later, once hemodynamic stability is achieved, RRT is shifted to intermittent hemodialysis (IHD). Those with AKI stage 3 frequently have MOF related to sepsis or trauma and are ventilator dependent. Nutrition support in patients with AKI stage 3 often becomes a highly individualized regimen tailored to the critically ill but also reflecting needs specific to the prescribed RRT modality.

Energy/Protein

The initial research debunking the idea that those with AKI required energy intakes as high as 50 kcal/kg was done nearly 20 years ago [12,13]. Soop et al. [13] reported an energy expenditure (EE) that was 128% of the basal energy expenditure (BEE) in patients with MOF and AKI requiring RRT. In those in MOF with only mild AKI or without AKI, EE was 142% of BEE. The lower EE in AKI requiring RRT was attributed in part to an 8% loss of the EE of normally functioning kidneys. Schneeweiss et al. [12] found that AKI with septicemia produced an EE 128% of BEE, whereas those with AKI but who were not septic had an EE 105% of BEE, which was not significantly different from normal controls. Sepsis and/or MOF occurring with AKI appeared to increase EE 130% to 140% over BEE, which did not differ from other critically ill populations without AKI. In the mid-1990s, Macias et al. [14] observed optimal outcomes with 25 to 35 kcal/kg for those on CRRT. In 2005, Fiaccadori et al. [15] reported tighter glucose, lower triglycerides, and less insulin use when subjects with AKI were fed 30 kcal/kg compared with 40 kcal/kg with isonitrogenous parenteral nutrition (PN). Following these studies, the recommended energy intake for stage 3 AKI has drifted downward, closer to that commonly used for the critically ill; most recently, Druml [16] recommended 20 to 30 kcal/kg, never to exceed 30 kcal/kg in critical illness.

During the 1970s, essential amino acids (EAAs) were fed parenterally with hypertonic dextrose in AKI, in an attempt to control muscle catabolism and avoid RRT [17–19]. The specific nutrition support prescription included EAAs, 12 g, and dextrose with vitamins, 350 g [20]. That practice was discontinued in favor of earlier, more aggressive RRT and nutrition support with a mix of EAAs and nonessential amino acids (NEAAs). Also, several amino acids normally recognized as NEAAs (including histidine, tyrosine, arginine, serine, and cysteine) become essential in AKI, making EAA formulas an incomplete nitrogen source [16,21]. There remains no indication for the use of EAAs at any stage of AKI.

Once IHD is initiated in AKI, the recommended protein intake becomes the same as that for patients with CKD on IHD at a minimum of 1.2 g/kg and up to 1.5 g/kg [22–25]. The technology

of RRT has advanced to provide sufficient clearance of nitrogenous wastes, therefore allowing the higher protein requirements of critical illness with its associated hypercatabolism. Initial research examining protein requirements with CRRT advised intakes in the range of 1.5 to 1.8 g/kg [14]. Frankenfield et al. [26] observed amino acid losses in CRRT to be directly related to effluent rate through the CRRT filter. Accordingly, others suggested an additional 0.2 to 0.35 g protein/liter of effluent be added to the recommended protein requirement for IHD to correct for the additional protein loss with CRRT [25,27]. Scheinkestel et al. [28] simplified the estimation of pro- tein needs with CRRT, and reported that protein intake greater than 2.0 g/kg and up to 2.5 g/kg was necessary for a positive nitrogen balance. Survival in this study rose by 21% for every 1-g increase in nitrogen intake.

Fluid and Electrolytes

Volume overload and the lack of effective and safe fluid removal in AKI once prohibited the administration of adequate nutrition support. With the increasing availability of CRRT over the past 30 years, it became possible to give the fluid volume needed for a full nutrition-support prescription. Sufficient volume removal is also possible with IHD to permit adequate nutrition support. Daily IHD is sometimes prescribed to achieve the desired volume removal and permit the necessary nutrition support.

Hyperkalemia in AKI is the result of impaired excretion and catabolism. Rhabdomyolysis, gastrointestinal bleeding, and uncorrected acidosis may also contribute. Potassium dialysate concentration is prescribed according to the predialysis serum potassium and desired clearance. The dialysis prescription should be carefully assessed in relationship to daily laboratory values and the potassium contained in nutrition support. If supplemental potassium is needed, bolus rather than continuous infusion with PN is preferred.

Calcium and Phosphorus

Although hyperphosphatemia is more frequently observed, hypophosphatemia can also occur. A loss of renal excretion and concurrent hypercatabolism contribute to elevations in serum phosphorus. Nutrition support with IHD usually requires the minimal phosphorus intake with phosphate-binding medication. Occasionally, hypophosphatemia is observed with IHD, and is related to refeeding and a pre-existing history of malnutrition. Phosphorus intake should then be liberalized and/or phosphate binders discontinued. Continuous removal of phosphate occurs with CRRT; therefore, serum phosphorus must be monitored closely and losses replaced to avoid hypophosphatemia. A correction is made with bolus doses of sodium phosphate, 20 mmol, to attain serum phosphorus less than 3.0 mg/dL.

Multiple factors can cause hypocalcemia in AKI; some are associated with the loss of renal function or RRT and others with the course of the critical illness. Hyperphosphatemia binds calcium, as does the citrate that is present as a preservative in blood products for those requiring multiple blood transfusions. In patients with rhabdomyolysis, calcium is sequestered by damaged

muscle tissue, which causes serum ionized levels to decrease. Diminished activation of 1,25-dihydroxy vitamin D3 with the loss of functional renal mass may inhibit calcium absorption in the gut. Calcium loss in the CRRT effluent can be significant and a continuous calcium infusion is required with CRRT to correct losses [29]. The standard calcium concentration for IHD is 2.5 meq/L, which equates to a serum ionized level of 1.25 mmol/L and can provide an intradialytic source of calcium. Hypercalcemia arises less frequently but can occur if hyperparathyroidism or malignancy is present.

Micronutrients

The literature discussing the effects of critical illness or iatrogenic therapy, such as RRT, on micronutrient status often refers to low serum markers of micronutrients as indicators of deficiency. Such information must be interpreted with caution where the acute phase response is active, because inflammation induces a redistribution of micronutrients, invalidating serum markers [30,31]. Where micronutrient losses have been studied and can be estimated reliably, as with IHD or CRRT, then a dose for replacement can be suggested.

Water-soluble vitamins have a low molecular weight that permits their removal with RRT. The CKD population receiving chronic IHD is prescribed a daily water-soluble vitamin replacement. Water-soluble vitamin loss in AKI on RRT has not been studied, but it is unlikely that these losses differ from IHD in CKD. Replacement doses are similar to those stated in the Dietary Reference Intakes (DRI) [32]. Folate and pyridoxine are exceptions, and are replaced above the DRI at 1 mg and 10 mg, respectively. Vitamin C should be limited to 100 mg with IHD, or less than 200 mg with CRRT, because it is converted to oxalate, a recognized toxin in renal failure [24,25,33]. The removal of oxalate by RRT is not adequate [34]. Oxalate accumulation in the renal tubules can occur with large doses of vitamin C during oliguric or anuric AKI, adding to the existing AKI and reducing the possibility of renal recovery [35,36].

Conflicting reports regarding vitamin A, specifically retinol, are found in the literature on AKI. Retinol is known to accumulate in CKD and the elevation is attributed to the loss of renal degradation of retinol-binding protein. Hypercalcemia is the most frequently reported retinol toxicity symptom in CKD. Accordingly, renal-specific vitamins are formulated without retinol. Druml et al. [37] found depressed serum retinol with normal retinol-binding protein levels in AKI. However, serum retinol has been inversely related to C-reactive protein during inflammation [30]. Gleghorn et al. [38] observed elevated serum retinol with hypercalcemia in AKI when retinol, 1500 μg/d, was given in PN. The hypercalcemia resolved once the retinol was removed. Given the potential for toxicity, retinol dosing should be done cautiously in AKI. Limiting retinol to the DRI of 700 to 900 μg/d, as recommended for nutrition support in CKD, may be advisable in AKI as well.

Trace elements are well known for positive or negative acute phase reactant activity, making their serum values invalid in critical illness, including AKI stage 3. However, their loss and uptake related to CRRT in AKI has been examined and offers some insights into dosing. Fluids

used in CRRT are parenteral and can be sources of trace element contamination. Berger et al. [39] reported a positive zinc balance from zinc contaminant in CRRT replacement fluid. Klein et al. [29] also found positive zinc balance during CRRT from zinc contaminant in the citrate anticoagulant. With the potential for zinc uptake from CRRT fluids, supplemental zinc beyond that contained in standard nutrition support should be avoided if no significant gastrointestinal losses are present.

Selenium in CRRT fluids is negligible but losses in CRRT effluent have been observed in the range of 35 to 91 μg/d [39,40]. This amount is at or exceeds the DRI as well as the recommended parenteral intake of selenium [41]. Cumulative losses of selenium via CRRT are likely to result in deficiency if not corrected. A suggested correction dose in addition to that supplied in standard nutrition support is 100 μg/d.

Copper does not appear to be a contaminant in CRRT fluids [42]. Effluent losses of copper during CRRT are about 400 μg/d [39,40]. This is nearly 50% of the DRI and falls well within the recommended parenteral intake range of 300 to 500 μg/d [41]. Multitrace element preparations containing 1000 μg per dose are available and represent an option to counter CRRT losses. Another concern is hepatic dysfunction with cholestasis occurring with AKI stage 3 and CRRT as part of MOF. Copper is withheld from nutrition support when the total bilirubin is greater than 3.0 mg/dL. Omitting copper with concurrent CRRT losses has the potential for a negative copper balance. If CRRT continues with cholestasis over the long term, it may become necessary to add copper back to the nutrition support to avoid deficiency.

Recovery Phase

The recovery phase of AKI is marked by polyuria. Diuresis can exceed 150 to 200 mL/h. Kidneys regaining function are unable to produce a concentrated urine, risking volume depletion and recurrent AKI. Careful attention to maintaining intravascular volume is essen- tial. When oral intake is inadequate or not possible, intravenous fluid as either 0.25 normal saline and 5% dextrose or 5% dextrose, at rates to match urine output, is often necessary.

Close monitoring of electrolytes and serum phosphorus is necessary to detect and treat depletion during recovery. Repletion protocols discontinued during the RRT phase of AKI may need to be reinstated and/or electrolytes (eg, potassium) added to maintenance intravenous fluids.

Nutrition support should include an energy intake of at least 25 kcal/kg and up to 35 kcal/kg, as needed, once mechanical ventilation is discontinued. Druml [16] recommended protein, 1.0 to 1.3 g/kg, once the polyuric or recovery phase of AKI has begun. Meeting adequate calorie and protein needs may often involve coordinating transitional feeding between two routes of nutrition support.

Delivery of Nutrition Support

National and international guidelines recommend enteral nutrition (EN) as the route of first choice when delivering specialized nutrition support [43,44••]. EN, either orally or via tube feedings, offers the advantages of gastrointestinal stimulation and villi preservation. Optimal oral intake is preferred in AKI patients. Calorie-dense oral supplementations may be used to enhance the patient's ability to meet nutritional goals. However, when patients are unable to consume adequate nutrition, tube feedings may be implemented. In an observational study by Fiaccadori et al. [45], EN-related complications and the adequacy of nutrient administration during 2525 days of EN were compared in 247 consecutive patients fed exclusively by the enteral route (65 normal renal function, 68 AKI not requiring RRT, 114 AKI requiring RRT). The investigators found no difference in gastrointestinal or mechanical complications between AKI patients and patients with normal renal function, except for high gastric residual volumes (not defined), which occurred in 3.1% of patients with normal renal function, 7.3% of patients with AKI not requiring RRT, 13.2% of patients with AKI requiring RRT ($P = 0.02$ for trend), and for nasogastric tube obstruction: 0.0%, 5.9%, 14%, respectively ($P < 0.001$). EN was safe and effective in patients with AKI. In patients experiencing intolerance to gastric feedings, clinicians are encouraged to try small-bowel feedings [45].

PN should be reserved for patients with impaired gut function or patients who are unable to tolerate small-bowel feedings. The combination of PN and EN has been safely administered, and is recommended, in patients unable to meet their nutritional requirements adequately using EN only.

Controversy surrounds the use of intradialytic parenteral nutrition (IDPN) in chronic hemodialysis patients; information is limited and investigation has been inadequate. Furthermore, no data exist for use of IDPN in AKI patients. Two studies identified acutely ill patients in their reviews [46,47]. Both studies were nonrandomized, observational studies reporting on limited, small sample sizes (18 and 8 patients). Additionally, the "acutely ill" patients were chronic hemodialysis patients admitted to the hospital for acute complications. Moreover, although the studies reported safe use of IDPN, no improvement in outcomes with the implementation of IDPN could be determined because neither investigator used a control group [46,47].

The only prospective, randomized, controlled trial to address the effect of IDPN on morbidity and mortality in malnourished hemodialysis patients in an intention-to-treat design was performed by Cano et al. [48•]. In this trial, 93 patients were randomly assigned to receive IDPN at each hemodialysis session for 1 year, and 93 were considered as control subjects and did not receive IDPN. Both groups received oral supplementations. The control and IDPN groups exhibited similar improvements in nutritional status. The mortality rate did not differ between the two groups (42% over 2 years). Similarly, hospitalization rates and changes in Karnofsky score were not influenced by the addition of IDPN. There was a tendency to a decrease in survival from months 12 to 24 in patients with diabetes in the IDPN group. The proposed explanation for

this trend was IDPN-associated hyperglycemia and its resulting complications. In both groups, body mass index, serum albumin, and prealbumin increased during oral supplementation without additional effect from IDPN. Importantly, this was the first study to show that improvement in prealbumin during nutritional therapy was associated with a decrease in morbidity and mortality in malnourished hemodialysis patients. The investigators concluded that the use of IDPN showed no apparent value over standard nutrition therapy with oral supplementation. With the lack of investigation specific to the AKI patient and no prospective, randomized trials demonstrating any benefit, the use of IDPN cannot be recommended in the patient with AKI [48•].

Conclusions

Critically ill patients with AKI complications are hypermetabolic and hypercatabolic. Appropriate, timely, and adequate nutrition support is required. Electrolyte, vitamin, and trace element adjustments are based on the patient's underlying complication and stage of AKI. EN is preferred but when EN is contraindicated or fails to adequately meet the patient's nutritional goals, PN should be administered. IDPN has no role in patients with AKI.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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have been highlighted as:
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This article reports the most current international nutrition guidelines from the European Society for Parenteral and Enteral Nutrition for patients with acute kidney injury. The article methodically discusses and grades nutrition support recommendations based on reported studies.

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This is the first preceptive, randomized, controlled, intent-to-treat study performed evaluating the utilization and appropriateness of IDPN based on patient morbidity and mortality.