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Nutritional Support for Patients with Acute Kidney Injury: How Much Protein is Enough or Too Much?

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Acute kidney injury occurs commonly in critically ill patients and is associated with increased morbidity and mortality in the ICU. The hypermetabolic and hypercatabolic state that occurs in ICU patients with acute kidney injury is distinctly different than other forms of renal failure such as chronic kidney disease and requires an approach to nutrition that supports protein synthesis to prevent severe muscle wasting and malnutrition. Protein restriction does not appear to offer metabolic advantages or decrease urea generation in AKI associated with critical illness, but does result in a more negative nitrogen balance with potential to compromise lean muscle mass and nutrition status. The metabolic studies available provide insight into appropriate calorie and protein requirements for critically ill patients with AKI.

INTRODUCTION

Acute kidney injury (AKI) occurs in approximately 7% of all hospitalized patients and between 33% and 66% of all intensive care unit (ICU) patients, depending on the definition of AKI (1–3). Formerly called acute renal failure, AKI is now the preferred terminology to better reflect the full spectrum of pathology and clinical presentation from organ compromise to failure (4). This change in terminology also reflects recent evidence that has linked rises in serum creatinine as small as 0.3 mg/dL with adverse outcomes (5). This suggests that clinicians must be vigilant for small changes in renal function and not just focus on overt failure. In the most generic sense, AKI is an abrupt decline in glomerular filtration rate (GFR) traditionally measured by rises in serum creatinine. In the extreme, AKI can lead to significant falls in the clearance of solutes resulting in uremia, disturbances in acid-base, electrolytes and fluid balance. As opposed to chronic kidney disease, in AKI there is often a hypercatabolic milieu as well as poor adaptation to the uremic state. This is an important dis-

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Table 1.
The RIFLE and AKIN Criteria for the Diagnosis of AKI (adapted from references 6,7)

RIFLE Class		
Risk	Serum creatinine increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 ml/kg/hour for 6 hours
Injury	Serum creatinine increase to 2.0-fold or GFR decrease >50% from baseline	<0.5 ml/kg/hour for 12 hours
Failure	Serum creatinine increase to 3.0-fold or GFR decrease >75% from baseline or serum creatinine >4 mg/dL with an increase of at least 0.5 mg/dL	Anuria for 12 hour
AKIN Stage		
1	Serum creatinine increase ≥0.3 mg/dL or increase to 1.5 to 2.0-fold from baseline	<0.5 ml/kg/hour for 6 hours
2	Serum creatinine increase >2.0 to 3.0-fold from baseline	<0.5 ml/kg/hour for 12 hours
3	Serum creatinine increase >3.0-fold from baseline or serum creatinine >4.0 mg/dL with an increase of at least 0.5 mg/dL or need for dialysis	<0.3 mg/kg/hour for 24 hours or anuria for 12 hours or need for dialysis

tinction as the treatment imperatives in the patient with AKI differ from those in a patient with CKD. This is especially true in terms of nutritional support.

There have been a number of definitions of AKI in the literature, which have made it difficult to compare different populations and outcomes reported in various studies (5). In 2002, the Acute Dialysis Quality Initiative proposed a definition of AKI specifically for critically ill patients based on serum creatinine and urine output known as the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) classification (Table 1) (6). The RIFLE criteria initially described three grades of severity and two outcome classes, but the Acute Kidney Injury Network (AKIN) provided further modification with 3 stages based on smaller incremental changes in serum creatinine and urine output and established a time component to the definition of AKI (Table 1) (7). A current consensus definition of AKI is an abrupt reduction (within 48 hours) in kidney function with an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL (26.4 Mmol/L), an increase in serum creatinine of >50% (1.5-fold from baseline), or a reduction in urine output (<0.5 mL/kg/hr for >6 hrs) (7). These criteria can diagnose AKI with high sensitivity and specificity and describe different severity levels that have prognostic value for affected patients (8). However, these definitions are largely dependent upon rises in serum creatinine, which is a late occurrence in the pathogenesis of AKI. Thus, numerous biomarkers of AKI are in advanced stages of development that aim to provide more timely and accurate diagnosis of AKI as well as improved prognostic information (9).

Despite advances in critical care, approximately 2 million people worldwide will die this year from AKI (4). Those patients with the most severe form of AKI (those needing renal replacement therapy) will have 90-day mortality rates as high as 52.5% (10). The reasons for this extremely high mortality associated with AKI is not clear and likely involves numerous factors such as the intrinsic effect of AKI on outcomes as well as indirect effects that loss of kidney function may be associated with such as alterations in drug dosages, limitations on diagnostic testing and provision of adequate nutrition. This review will focus on nutrient metabolism in AKI as well as provide an in-depth focus on the provision of nutritional support in this vulnerable population. It is only through a comprehensive therapeutic plan including nutritional support that the mortality associated with AKI can be attenuated.

NUTRIENT METABOLISM IN AKI

Calorie Expenditure

Metabolic rate does not appear to be directly influenced by the presence of AKI *per se*; instead calorie expenditure is dictated primarily by the severity of the underlying illness. Energy expenditure can be influenced by renal replacement therapies (RRT) such as hemodialysis or continuous renal replacement therapy (CRRT).

Energy needs can be increased due to the heat that is lost as blood travels through the dialysis circuits, or the inflammatory response that arises when blood comes in contact with hemodialysis membranes used as blood filters. (11 Druml 1999) However, the increased calorie needs created by heat loss or inflammation associated with RRT is at least partially offset by the calorie contribution when buffer agents (chemicals in the dialysate that are used to treat the metabolic acidosis associated with AKI) such as citrate and lactate, provided during RRT enter metabolic pathways as energy substrates (11,12). The chemical content of CRRT dialysate and/or replacement fluids can also influence energy balance. If the CRRT dialysate does not contain glucose, then the osmotic gradient can result in the loss of blood glucose into the dialysis fluids (13,14). Daily glucose losses into the dialysate fluid can range from 200–400 calories/24 hours depending on the blood glucose concentration of the patient (13,14). On the other hand, significant uptake of calories can occur with a glucose-rich (200 mg/dL) dialysate solution, with as much as 50% of the glucose in the dialysate being delivered to the patient depending upon the gradient for flow (13,14). The use of limited amounts of dextrose in the dialysis solution and dextrose-free replacement fluids will result in minimal calorie loss or delivery during CRRT. Most facilities have abandoned the use of dextrose-rich dialysate or replacement fluids, but practices vary worldwide and clinicians should be aware of the potential for calorie accrual or loss from RRT based on the practices at their own facility.

Protein Metabolism

Traditional education for diet therapy in chronic kidney disease (CKD) has highlighted the possibility of delaying the need for renal replacement therapy with adequate provision of calories while restricting dietary protein to as low as 0.3 grams of protein/kg/day along with supplemental keto-acids (15). There is a natural inclination to apply these same nutrition principals to nutritional support in AKI. However, it is important to remember that AKI invariably occurs in the setting of critical illness or injury, and thus the basic metabolic response to calories and protein in ICU patients with AKI is quite unlike the metabolism of patients with CKD.

In the acute stage of critical illness or injury, the cytokine and hormonal milieu results in unavoidable protein catabolism, even when full calories are provided (16,17). The insulin resistance and gluconeogenesis that persist in the fed state are hallmarks of critical illness or injury, meaning that further calorie increase will not necessarily result in further protein sparing. Although there is a state of net protein breakdown in the critically ill patient due to catabolism of skeletal muscle, whole body protein synthesis is actually increased in critical illness, in part due to increased hepatic protein synthesis of acute phase proteins (18). Most important to the discussion of nutrition support in critical illness and AKI is the fact that providing protein to the ICU patient further stimulates whole body protein synthesis. A series of classic studies demonstrated that provision of calories and protein in sepsis, trauma and burns stimulates whole body protein synthesis without significantly increasing whole body protein catabolism (19,20,21). Although net catabolism is not completely reversed by protein and calories in the early stage of critical illness, nitrogen balance is significantly improved compared to unfed patients.

Metabolic disturbances specific to AKI can exacerbate the catabolism of critical illness. Acidosis increases the breakdown of muscle protein by stimulation of the ubiquitin-proteasome system in muscle, which is one of the primary pathways of protein catabolism (22). Compounding this is the fact that RRT results in the loss of protein, peptides and amino acids into the dialysate, with the amount lost dependent on the dialysis method. Hemodialysis results in a minimal loss of protein, however, significant loss of amino acids (6–12 grams) and peptides (2–3 gms) per dialysis session can occur (2). The loss of protein and amino acids during CRRT depends on the technique (convection or ultrafiltration vs diffusion or dialysis) and the daily dose of dialysis or ultrafiltration. Protein loss during CRRT can vary from 1.2 to 7.5 gms/24 hours with an additional loss of amino acids equivalent to 6–15 gms/day (11,23). Increasing the protein provision for patients receiving CRRT is typically well tolerated as fluid overload or uremia during CRRT is uncommon. However, some clinicians hesitate to increase the protein provision for patients receiving intermittent HD, or non-dialyzed patients with AKI due to concerns of exacerbating uremia or furthering volume overload.

Several investigators have reported on the results of providing increased protein to patients with AKI that optimizes nitrogen balance, or may lead to increased generation of nitrogenous metabolites that can result in uremia (24–27). Although there are no large randomized studies that have investigated the effect of different protein intakes on patient outcome, a review of the available data and the study limitations can provide insight into what may be the best protein intake for patients with AKI.

DATA REGARDING NUTRIENT PROVISION IN AKI

An early study into the effects of different nutrition regimens in AKI reported the urea nitrogen appearance in patients receiving a low-protein parenteral nutrition (PN) (42 g protein) vs. PN with increased protein (78 gm). The average urea nitrogen appearance was not significantly different between the two groups, but the group receiving increased protein had improved nitrogen balance (24).

An observational study of 40 intensive care unit patients receiving CRRT reported on the effects of the nutrition regimen on urea appearance and protein catabolic rate (PCR) (25). The protein catabolic rate would reflect the degree of oxidation of proteins and can be viewed as a surrogate marker for the degree of uremia that anuric patients with AKI would have if not dialyzed. The investigators evaluated the actual amounts of nutrition received by the patients and did a regression analysis adjusted for within-person correlation and the previous days PCR. The study reported that the average normalized protein catabolic rate (nPCR) was 1.4 ± 0.5 gm protein/kg/day. Interestingly, those patients that received a low protein intake (0.7 gm protein ± 0.2 gm/kg) did not have a significantly different urea appearance rate or nPCR compared to those patients that received increased protein (1.3 ± 0.2). The nPCR of the low protein group was 1.4 ± 0.4 g/kg while the nPCR in the group receiving increased protein was 1.5 ± 0.5 g/kg. However, those patients that received the lower protein intake had a greater negative nitrogen balance than the patients receiving increased protein (–8.4 ± 4.9 versus –3.5 ± 4.3 respectively).

Macias et al also reported on the effects of an even higher protein intake of 2.0 g/kg/day. Patients that received 2.0 g protein/kg had improved nitrogen balance compared to those receiving 1.5 g protein/kg, but increasing protein to 2.0 g protein/kg did lead to increased nPCR. The amount of calories provided also appeared to influence nPCR and nitrogen balance. Those patients with decreased protein intake (0.6–0.8 g/kg) had decreased nPCR and improved nitrogen balance when calories were increased from 10–15 calories/kg to 30 calories/kg. However those patients receiving increased protein did not benefit from increasing calories above 30 calories/kg, and those patients that were overfed (40–60 calories/kg) had increased nPCR and decreased nitrogen balance. There was no information provided regarding adequacy of glucose control during the study, and thus it remains unknown to what extent the increased protein catabolism with overfeeding was related to hyperglycemia.

The limitations of this study include the observational design, where patients were not randomized to a nutrition regimen, and differing patient characteristics could have influenced both the caregivers' decisions on nutrition regimen and their metabolic status. Additionally, the methods of adjusting for the previous day's nPCR does not account for the possibility that a patient's metabolic status may change with time, becoming less catabolic as they improve, or acutely more catabolic from a new nosocomial infection or complication. Despite these limitations, the results imply that the response to protein intake and restriction in AKI is consistent with the findings reported in other critically ill populations: increased protein appears to be utilized. Decreased protein intake only resulted in more muscle protein breakdown with essentially the same generation of urea as those patients receiving moderate intakes of protein. Further increases in protein intake above 1.5 g protein/kg may lead to increased urea generation, and increasing calories beyond energy expenditure may lead to increased protein breakdown and a more negative nitrogen balance.

A more recent observational study has reported results similar to Macias et al regarding the average protein turnover in ICU patients receiving CRRT. Ganesan et al reported that the mean nPCR in 25 mixed ICU patients receiving CRRT was 1.57 ± 0.4 g/kg/day. (26) Patients received a relatively low protein intake of

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0.56 ± 0.38 g/kg/day, which resulted in an average protein balance of –1.0 ± 0.6 g per kilogram of body weight. These results imply that a 150 lb patient with AKI receiving CRRT would have a daily 68 g protein deficit while they are on a restricted protein intake.

The data reviewed above suggests that protein restriction does not decrease urea appearance or PCR in critically ill patients with AKI. Additionally, it appears that a modest increase in protein intake in AKI improves nitrogen balance without significantly increasing urea generation. Nevertheless, it is apparent that very large increases in protein intake (which exceed the body's synthetic capacity) would have the potential to increase urea generation and potentially worsen uremia.

Several studies have investigated increased protein intake in patients receiving CRRT in an attempt to improve nitrogen balance and study the effects of increased protein on urea generation. A study of critically ill patients with AKI receiving CRRT compared two consecutive cohorts receiving the same calories, but variable amounts of protein. (27) The first group received an average protein provision of 1.2 g/kg/day while the second group received 2.5 g/kg/day. Patients receiving 1.2 g protein/kg had mean nitrogen balance of –5.5 g/day, while the patients receiving 2.5 g protein/kg had a less negative mean nitrogen balance of –1.92 g/day, but the difference in mean nitrogen balance was not statistically significant. Patients receiving 2.5 g protein/kg were significantly more likely to experience a positive nitrogen balance during any 24-h period than the patients receiving 1.2 g protein/kg (53.6% vs. 36.7%). However the patients receiving increased protein also required more aggressive hemofiltration to maintain control of uremia compared to the moderate protein group (mean ultradiafiltrate volume: 2145 mL/h vs. 1658 mL/h), and had a significantly higher mean plasma urea level (26.6 mmol/L vs. 18 mmol/L). These results suggest that increasing protein from 1.2 to 2.5 g/kg allowed modest improvements in nitrogen balance, but a protein intake of 2.5 g/kg resulted in increased urea generation and increased need for intensification of dialysis.

A randomized study of 50 critically ill ventilated patients who required CRRT investigated the effect of progressive increases in protein intake (28). One group of 10 patients who received 2.0 gm protein/Kg for the entire study period served as a control group. The other group received progressive increases in protein intake, starting at 1.5 gm protein/Kg for 2 days, then 2.0 gm/Kg for 2 days, and finally 2.5 gm/Kg for 2 days. All patients were studied for six days total, and received calories that met their measured (or estimated, if metabolic cart not possible) energy expenditure (an average of 34 calories/Kg). Nitrogen balance was measured on days 2, 4, and 6 by analyzing the nitrogen in the dialysate fluid (and urine if the patient made >500 ml/day). The investigators reported that nitrogen balance was positively related to protein intake and that a positive nitrogen balance was more likely to be attained with protein intakes larger than 2 g/kg/day. The nitrogen balance became positive in the study group patients over time but was negative in control patients over time. The authors also reported that a positive nitrogen balance was associated with improved survival, but that on multi-variant analysis the protein intake was not significantly associated with improved survival. The major limitation of this study was that the patients were only studied for 6 days, and were maintained at each protein level for 2 days. There was inadequate time to reach equilibrium at each new protein intake. It is possible for a patient to transiently appear in positive nitrogen balance if measurements are made immediately after an increase in protein. It is important to note that that the "control" group who received 2.0 gm protein/kg each day had an increasingly negative balance over the 6 days. On day 4 of the study, when both groups were getting the same nutrition (2.0 gm protein/Kg), the controls had a nitrogen balance of negative 7 g, and the group who had just had their protein increased to the same level had a positive 0.4g nitrogen balance.

One study has investigated the effects of protein intake on patients with less severe non-oliguric AKI, not yet requiring RRT (29). Singer et al randomized 14 critically ill patients with AKI that required parenteral nutrition, had a creatinine clearance <50 mL/minute and furosemide-induced diuresis >2000 mL/24 hours. All patients received 2000 non-protein calories (dextrose and lipid emulsion) and received either 75 gm protein (normal protein) or 150 gm protein (high protein). The results demonstrated that there were no significant differences between the blood urea nitrogen and the need for dialysis between the two groups.

Patients receiving increased protein had a significantly more positive cumulative nitrogen balance (–10.5 ± 17 g/day vs. 9 ± 8.3 g/day, less positive fluid balance (2003 ± 1336 mL vs. –2407 ± 1990 mL), and lower furosemide requirement (1003 ± 288 mg vs. 649 ± 293 mg) compared to the low protein group respectively. Naturally this study is far too small to evaluate patient outcomes such as mortality, but the results are consistent with previous data above that a moderately increased protein intake appears to be utilized by critically ill patients, improves nitrogen balance, and does not lead to increased urea generation. The major limitation of this study was the absence of any height, weight or BMI information on any of the patients preventing the calculation of the grams of protein/kg received by the patients, therefore it is not possible to assess the appropriateness of the calorie level or protein load for individual patients, or to compare the two groups in terms of protein given per kilogram.

There are few studies that have only investigated the effect of different calorie intakes on protein turnover or urea generation in AKI. Fiaccadori et al studied the effect of low versus high calorie PN in critically ill patients with AKI that required daily hemodialysis or sustained-low efficiency dialysis (17). Patients received 24 hours of protein-free PN (D20) and then PN with either 30 calories/kg (low-calorie) or 40 calories/kg (high-calorie). After 3 days on one calorie level patients were crossed over to the opposite regimen for an additional 3 days. All of the patients in both groups received the same protein of 1.5 g/kg. The results demonstrated no significant difference in nitrogen balance, PCR or urea generation rates between the low-calorie and high-calorie PN groups. However there was a significantly increased insulin requirement, serum blood sugar, and serum triglyceride level in the high-calorie PN group. These results suggest that 30 calories/kg was meeting or exceeding calorie expenditure for most patients and that 40 calories/kg was exceeding calorie needs for many or most patients. Also of interest in this study is the observation of the metabolic changes that occurred when patients transitioned from receiving 20 calories/kg of dextrose alone to a regimen containing full calories and 1.5 gm protein/kg. Not surprisingly, mean nitrogen balance improved from –15.47 on dextrose with no protein to +1.08 with full calories and protein. Most notable however, is the fact that increasing protein intake from 0 to 1.5 g/kg did not significantly increase protein catabolic rate (1.37 to 1.47 g/kg/day) or urea generation rate (21.0 to 23.8 mg/min). These results are consistent with those of previous studies that demonstrate no advantages and potential negative sequelae from overfeeding, and that critically ill patients appear to utilize protein to a range of approximately 1.5 g/kg without increasing urea generation.

TRANSLATING THE DATA: BRINGING THE RESEARCH DATA TO BEDSIDE

The best available data indicate that there is no metabolic advantage for a protein restriction in AKI, and that moderate increases in protein intake improve nitrogen balance. To date there is no robust data from large randomized trials that demonstrate improved outcome in terms of morbidity or mortality for a specific nutrition regimen in AKI. However, patients admitted with compromised nutrition status, or those with extended hospitalizations and patients at increased risk for functional impairments from muscle loss such as the elderly and those with morbid obesity cannot afford to have exaggerated muscle loss from extended negative nitrogen balance. Unfortunately, in the clinical setting it is not uncommon for healthcare providers to request a decrease in protein provision when faced with new onset AKI or increasing uremia in a critically ill patient. It is important to be able to recognize other contributors to uremia and troubleshoot nutrition issues that may play a role (see Table 2).

Calorie Provision

When evaluating nutrition issues that may relate to increasing uremia, the first step is to quantify how much nutrition was actually received by the patient. In patients that are receiving enteral nutrition (EN) it is well documented that patients frequently do not receive the full ordered amount of feeding (30–32).

EN is frequently held prior to diagnostic tests, line insertions, lost access, real and perceived feeding intolerance, hypotensive episodes on and off dialysis, among others (31–33). We have commonly encountered the scenario where a decrease in protein delivery was recommended due to increasing uremia, only to

Table 2.
Evaluation of Contributers to Uremia

- Evaluate *actual* amount of protein and calories delivered
  - Volume of enteral/parenteral feeding received?
  - Protein supplements actually administered?
- Evaluate glucose control
  - Other sources of calories (D5 drips, propofol)
- Evaluate calorie provision
  - Indirect calorimetry
  - Increased work of breathing/physical activity
  - Low BMI with increased lean mass/kg?
  - Malabsorption?
- Gastrointestinal bleeding
- Corticosteroids
- Intravascular volume depletion
  - Diarrhea
  - Diuresis
  - Enteral or parenteral feeding/flushes held or lost access?

find that the patient had received so little feeding that actual protein provision was closer to 0.3–0.6 g/kg, far less than what had been recommended. In cases of minimal nutrition provision, it is far more likely that this semi-starvation during critical illness exacerbated breakdown of skeletal muscle for fuel, and the most useful nutrition intervention would be more, rather than less nutrition. In situations of impaired glycogen synthesis or storage such as in severe cirrhosis, even short periods of starvation lead to substantial catabolism of lean muscle mass to meet the needs of cells that are glucose dependent. Catabolism of body proteins for oxidation as fuel has potential to be a much greater contributor to uremia than additional exogenous protein. Protein that is oxidized has the nitrogen group cleaved so the carbon base can be utilized for fuel, and the nitrogen subsequently excreted. Protein delivered with full enteral or parenteral calories can be used to support protein synthesis with only limited amounts oxidized due to the protein sparing effects of sufficient carbohydrate and lipid provision. An acutely ill patient that has depleted glycogen stores from a period of minimal nutrition has not "adapted to starvation" and thus will "burn" substantial amounts of body protein. Consider that an acutely ill adult patient of 68 kg with depleted glycogen stores can oxidize in excess of 90 grams of protein/day, with only a portion of the amino acid nitrogen re-utilized (18–21). Oxidation of 90–100 gms of protein/day is potentially a far greater contribution to uremia than an increase from 1.2 to 1.5gm of protein/kg of protein, which is a difference of only 20gm of protein in a "reference" patient of 68 kg. Additionally, in the setting of full feeding, the additional 20 g of protein can be utilized for increased protein synthesis rather than oxidation.

Providing appropriate calories is essential to avoiding excessive urea production, since both extreme underfeeding or overfeeding appear to contribute to increased protein oxidation. It is important to recognize that sedated mechanically ventilated patients may have a very modest energy expenditure that is closer to estimated resting energy expenditure (34). Likewise, some patients that are less critically ill, no longer sedated and engaged in tracheostomy collar trials with increased work of breathing, or participating in physical therapy, can have calorie expenditures much higher than resting energy expenditure. Indirect calorimetry can be invaluable if it is available. However, it is important to realize that in critically ill patients a *single* indirect calorimetry can have a greater error factor than many estimates of energy needs because energy expenditure in critically ill patients can change more than 30% each day (32). Although there is no data to establish how often indirect calorimetry should be repeated, the data indicates that indirect calorimetry would need to be repeated frequently to be meaningful, and clinicians should recognize the daily variability of calorie expenditure in critically ill patients when interpreting indirect calorimetry studies.

Low BMI

Patients with a very low BMI are at particular risk for underfeeding if energy needs are estimated rather than measured. Resting energy expenditure of patients with an average BMI of 15 were approximately 30–35 calories/kg of actual weight; lean patients do not have a surplus of endogenous fat calories to draw upon during periods of inadequate calorie supply (35,36).

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Hyperglycemia

Another factor than can lead to increased protein catabolism and thus urea production in AKI is inadequate glucose control. If serum glucose is consistently >200 mg/dl, the utilization of nutrition is impaired and increased catabolism of lean muscle mass will occur. Additionally, glucosuria results in lost calories resulting in an increase of protein oxidation for fuel. There is ongoing controversy regarding the optimum goal for glucose control in specific populations, and patients with AKI appear to be at increased risk of hypoglycemia during intensive insulin therapy, due in part to decreased renal clearance and longer half-life of insulin. It appears that the balance between the benefits of good glucose control and avoiding hypoglycemia is reached with intensive insulin therapy with goal blood glucose of 140–180 mg/dl in most critically ill patients (37).

Gastrointestinal Bleeding

Other sources of increased urea generation include gastrointestinal bleeding in the upper GI tract. Blood contains twice as much protein on a per-volume basis as most high nitrogen EN. While the volume of blood protein that is digested and absorbed in most cases of GI bleeding is less than that provided by nutrition support, the additional nitrogen added to feeding regimen can result in increased urea generation.

Corticosteroids

Corticosteroid administration results in increased gluconeogenesis and protein catabolism, and depending on the dose and clinical scenario can contribute to urea generation. Sufficient protein administration to optimize protein synthesis is advisable in patients receiving corticosteroids, but there is little advantage to excessive protein for patients on high-dose corticosteroids because catabolism cannot be completely reversed. Glucose control can be further compromised in patients receiving corticosteroids, and minimizing hyperglycemia may help limit catabolism of protein.

Malabsorption

Malabsorption that creates a calorie deficit and thus increased oxidation of protein to meet energy needs can also result in increased urea generation. Most critically ill patients digest and absorb standard polymeric EN without a problem. However, on occasion, patients may present with occult malabsorption from pancreatic exocrine insufficiency from past alcohol abuse or undiagnosed Crohn's or celiac disease. Malabsorption may occur without obvious diarrhea, especially in patients that are receiving narcotic pain medications that slow transit through the colon allowing increased water reabsorption. Patients suspected to have a malabsorptive process might benefit from a fecal fat analysis to confirm the diagnosis avoiding unnecessary use of an expensive elemental or semi-elemental formula.

Volume Status

Fluid volume status in the critically ill population is a major source of discussion and even contention in the ICU, especially during ventilator weaning. Successful weaning from mechanical ventilation is independently associated with a negative volume status in observational studies (38,39); hence an elevation in BUN is to be expected. The fluid and catheter treatment trial (FACTT) demonstrated that a conservative fluid management strategy in acute lung injury and acute respiratory distress syndrome resulted in improvements in the oxygenation index, the lung injury score and decreased time on mechanical ventilation and ICU length of stay. (40). Management of congestive heart failure entails similar challenges to ventilator weaning in terms of balancing the needs of the kidneys with the need for diuresis. However, in heart failure there is the added potential for marginal kidney perfusion at baseline due to the compromised heart function. While a conservative fluid strategy or need for diuresis can lead to a more concentrated intravascular volume with increased BUN, there is no reason and no benefit for providing inadequate protein due to this intentional intravascular concentration.

AREAS OF UNCERTAINTY

Current research has demonstrated the metabolic response to calorie and protein provision in mixed populations of critically ill patients with AKI. Providing protein at 1.3–1.5 g/kg did not increase urea

Table 3.
Estimation of Nitrogen Balance from PCR

PCR (protein Catabolic Rate in g/day) = [GUN + 1.2] × 9.35

G.U.N. (urea nitrogen generation rate):

Vu1 = dry body weight (kg) × 5.5 (Female)
or 5.8 (Male) = X deciliters

Vu2 = Vu1 + deciliters of water gain between BUN draws

BUN2 = 2nd BUN measurement

BUN1 = 1st BUN measurement

$$\frac{[BUN2 \times Vu2] - [BUN1 \times Vu1]}{\text{Time (minutes)}}$$

(dl of water change can be can be obtained from I/O sheets, derived from fluid removed from dialysis, or calculated from 24 hour weight change)

Example: Mrs. A is dialyzed M, W, F, and gets a BUN drawn at about the same time each morning. On Tuesday morning her BUN is 42 mg/dl and on Wednesday it is 85 mg/dl. She routinely has 2L fluid removed in the dialysis sessions every other day, including this particular Wednesday after the BUN draw. Her dry weight is 60 kg

Vu1 = 60 kg × 55% body water, or 330 dl

Vu2 = 330 dl + 10 dl fluid gain in 24 hrs = 340 dl

$$\textbf{GUN} = \frac{[85 \text{ mg/dl} \times 340 \text{ dl}] - [42 \text{ mg/dl} \times 330 \text{ dl}]}{1440 \text{ min}}$$

= [28900 mg – 13860 mg]/1440 min

= 15040 mg/1440 min = 10.4 mg/min

PCR = [10.4 + 1.2] × 9.35 = 109 g/day

- Patients that make over 250 mls of urine/24 hrs should have urinary nitrogen quantified and these losses added to that calculated from PCR.
- Add 4 gm/24 hours for obligatory stool and skin losses.

generation compared to a protein restriction when full calories were provided. Increasing protein to 2.0–2.5 g/kg improves nitrogen balance, but this improvement comes at the cost of increasing urea generation. Patients with large wounds, skin breakdown or burns generally receive 1.8–2.5 gm protein/kg to allow tissue repair, and these patients may require more frequent dialysis in order to maintain adequate protein intake.

One topic that is not adequately addressed by current research is the metabolic response to hypocaloric feeding with full protein in AKI. Obese patients with a body mass index (BMI) greater than 30 appear to benefit from hypocaloric feedings while providing increased protein (41). Studies of hypocaloric feeding in obese patients indicate that outcomes such as ventilator weaning are hastened, and that nitrogen balance and wound healing is not impaired compared to eucaloric feeding (41). Hypocaloric feedings can increase protein oxidation for fuel, and no studies have reported on the metabolic response to graded calorie and protein intakes in obese patients with AKI. In general, a modest degree of increased urea generation does not present a problem to patients receiving continuous or daily RRT. Those patients receiving intermittent RRT may require a calorie provision that is only mildly hypocaloric to prevent excessive uremia between dialysis sessions. There is a need for research that evaluates urea generation response to increased protein intake in critically ill obese patients receiving hypocaloric feeding. In the absence of full data our clinical approach is to provide 20–25 calories/kg adjusted weight and 2.0 g protein per kg of ideal weight for the short-term. In those patients with extended hospitalizations or where weight loss may be imperative to achieve ventilator weaning, we may incrementally decrease calories and evaluate changes in interdialysis labs. Although traditional nitrogen balance calculated from urinary nitrogen losses is not possible in oliguric patients, the urea generation rate can be calculated from urea accumulation in the blood adjusted for water accumulation in the patient and used to assess protein catabolic rate in patients receiving intermittent hemodialysis (42) (see Table 3 for calculations and an example of estimation of nitrogen balance from PCR). Obviously, when estimating fluid accumulation in a patient, factors such as I/O records or weight changes rely on accurate measurements and record keeping. Also, just like conventional nitrogen balance studies, finding out that a patient is in negative nitrogen balance does not automatically mean that additional protein provision is nec-

Table 4.
Nutrition Requirements of ICU Patients with AKI

Calories
Underweight: 35–45 Kcals/kg (post refeeding period)
Normal weight: 25–35 calories/kg
Obese: 20–25 calories/kg adjusted weight

Protein
Most ICU patients: 1.4–1.6 gm protein/kg
Burns/severe wounds: 1.8–2.5 gm protein/kg

essarily the correct response, since patients can be in negative nitrogen balance from an evolving infection, inadequate calories, poor glucose control, etc. Calculated protein catabolic rate does not take amino acid losses during dialysis or stool and skin nitrogen losses into account.

Another issue that is not adequately addressed by current research is the ideal protein provision for patients with extended duration of illness and recovery. Most studies of nutrition provision in AKI are short-term metabolic studies in critically ill patients and the results may not represent the metabolism of more stable patients with decreased rates of protein synthesis. Those patients that are no longer critically ill and have progressed into end-stage renal disease may have increased needs for wound healing or rehabilitation after the catabolism incurred while critically ill. Patients without wounds and post rehabilitation that do not regain renal function would have nutrition requirements similar to other maintenance dialysis patients. However, there is little to no data available on the impact of nutrition regimens on patients that are no longer critically ill and are experiencing slow recovery of renal function.

CONCLUSIONS

AKI associated with critical illness or injury is a hypercatabolic state that does not permit protein sparing, even when full calories are provided. Increasing calories beyond calorie expenditure provides no nutrition advantage and appears to exacerbate protein catabolism in the acute phase of illness. Metabolic studies provide data that average protein catabolic rate is 1.5 gm protein/kg, and RRT induces further amino acid and protein loss. A protein restriction does not decrease the production of urea in critically ill patients with AKI, and restriction of protein results in increased catabolism of lean mass with no change in urea generation or "protein load" delivered to the kidneys. Increasing protein intake above 1.8 gm/kg appears to increase urea generation, and may increase need for RRT. There is a need for studies that investigate the metabolic response to hypocaloric, protein-sparing feedings in obese patients with AKI, the metabolic response to protein provision with extended hospitalizations and decreased acuity of illness, as well as the effects of specific nutrition regimens on outcomes in patients with AKI. See Table 4 for nutrition requirements of ICU patients with AKI. ■

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Answers to this month's crossword puzzle:

B	I	L	I	A	R	Y	A	T	R	E	S	I	A	■
A	L	A	■	L	E	E	■	T	A	G	■	O	■	P
R	■	X	■	F	A	T	■	G	■	J	T	U	B	E
I	■	A	N	A	L	■	■	■	T	A	N	■	U	P
U	P	T	O	■	I	■	T	R	A	C	T	■	T	T
M	A	I	N	■	G	E	O	■	L	■	■	A	■	I
■	I	V	■	■	N	■	O	D	O	R	■	S	■	C
I	L	E	U	S	■	B	■	I	S	■	P	P	I	■
D	■	■	■	Q	U	A	■	Z	E	O	L	I	T	E
■	E	I	■	U	■	S	■	Z	■	F	A	R	■	C
F	L	U	M	A	Z	E	N	I	L	■	N	A	N	O
■	A	■	I	M	■	L	■	N	■	A	■	T	■	L
H	P	Y	L	O	R	I	■	E	G	D	■	I	S	O
U	I	■	■	U	■	N	O	S	■	D	■	O	R	G
E	D	G	E	S	■	E	N	S	■	S	U	N	■	Y