Amino Acid Requirements in Critically Ill Patients with Acute Kidney Injury Treated with Continuous Renal Replacement Therapy

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Acute kidney injury in critically ill patients is often a complication of an underlying condition such as organ failure, sepsis, or drug therapy. In these patients, stress-induced hypercatabolism results in loss of body cell mass. Unless nutrition support is provided, malnutrition and negative nitrogen balance may ensue. Because of metabolic, fluid, and electrolyte abnormalities, optimization of nutrition to patients with acute kidney injury presents a challenge to the clinician. In patients treated with conventional intermittent hemodialysis, achieving adequate amino acid intake can be limited by azotemia and fluid restriction. With the use of continuous renal replacement therapy (CRRT), however, better control of azotemia and liberalization of fluid intake allow amino acid intake to be maximized to support the patient's metabolic needs. High amino acid doses up to 2.5 g/kg/day in patients treated with CRRT improved nitrogen balance. However, to our knowledge, no studies have correlated increased amino acid intake with improved outcomes in critically ill patients with acute kidney injury. Data from large, prospective, randomized, controlled trials are needed to optimize the dosing of amino acids in critically ill patients with acute kidney injury who are treated with CRRT and to study the safety of high doses and their effects on patient morbidity and survival.

Key Words: renal failure, acute kidney injury, critical illness, continuous renal replacement therapy, CRRT, amino acids, nutrition.

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OUTLINE

The classic nomenclature "acute renal failure" is being replaced by the more current terminology "acute kidney injury," driven by the Acute Dialysis Quality Initiative (ADQI) group proposal for a consensus definition of acute renal failure. The ADQI consensus definition of acute kidney injury is denoted by the acronym RIFLE, which refers to three stages by increasing severity (risk, injury, failure) based on combined criteria of serum creatinine concentration or glomerular filtration rate and urine output, as well as two

outcomes (loss and end-stage kidney disease) in relation to kidney function.[1] In a retrospective study that used the RIFLE classification for the definition of acute kidney injury in the analysis of a database of 41,972 patients from 22 intensive care units (ICUs), patients with risk, injury, and failure had corresponding mortality rates of 20.9%, 45.6%, and 56.8%, respectively.[2] In a multinational, multicenter, prospective, epidemiologic survey of acute kidney injury in ICUs that included a total of 29,269 critically ill patients, 1738 patients (5.9%) developed acute kidney injury sometime during their ICU stay, including 1260 patients (4.3% of critically ill patients or 72.5% of patients with acute kidney injury) who were managed with renal replacement therapy (defined as peritoneal dialysis or any technique of renal support requiring an extracorporeal circuit and an artificial membrane).[3] Hospital and ICU mortality rates in patients with acute kidney injury who were treated with renal replacement therapy were 55% and 64%, respectively.[4]

Malnutrition is common in patients with acute kidney injury and is caused by anorexia, impaired protein metabolism and transport, oxidative stress, metabolic acidosis, nutrient losses through the hemodiafilter, and patient comorbidities. Because acute kidney injury in critically ill patients commonly occurs in the setting of other diseases, nutritional and metabolic changes are the result of underlying conditions such as surgery, trauma, burns, organ failure, and sepsis, rather than acute kidney injury alone. Proper nutrition is aimed at minimizing the effects of hypermetabolism and hypercatabolism and improving patient recovery.[5, 6]

Critically ill patients with acute kidney injury frequently have azotemia and fluid overload, and may not tolerate high fluid removal rates during intermittent hemodialysis over a 3–4-hour period. Patients who are managed with intermittent hemodialysis 3 times/week may need fluid restriction, and the ability to meet their higher amino acid requirements to compensate for hypercatabolism is often hindered by accumulation of nitrogenous waste. Although intermittent hemodialysis 3 times/week is common practice, critically ill patients with acute kidney injury may require more frequent intermittent hemodialysis to achieve metabolic and azotemic control. More frequent intermittent hemodialysis may allow more fluid intake depending on the patient's fluid status and tolerance. However, with continuous renal replacement therapy (CRRT), enhanced nitrogenous waste clearance and liberalization of fluid intake allow increasing amino acid intake to meet the patient's metabolic requirements. The preferred choice of dialysis in hemodynamically unstable patients is CRRT because it allows for slow continuous fluid removal and superior hemodynamic and metabolic control compared with intermittent hemodialysis.[7] There is wide variation with the modalities and types of renal replacement therapies used in hospitals, and available data on amino acid dosing in patients treated with CRRT are limited by study designs.

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Metabolic Effects of Acute Kidney Injury and Energy Requirements

Physiologic and metabolic functions of the kidneys include acid-base balance and regulation of fluids and electrolytes; excretion of metabolic end-products (e.g., urea), toxins, and drugs; production and secretion of enzymes (e.g., renin, angiotensin) and hormones (e.g., erythropoietin, vitamin D_3); and metabolic conversions (e.g., gluconeogenesis, lipid metabolism, ammoniagenesis). Significant changes to normal kidney functions occur with acute kidney injury that adversely impact the metabolic and nutritional status of the patient.[6]

The hypermetabolic and hypercatabolic responses to stress or injury affect the nutritional requirements of critically ill patients with acute kidney injury. The metabolic response causes increased production of stress mediators including cytokines (interleukin-1, interleukin-6, tumor necrosis factor-α), counterregulatory hormones (catecholamines, cortisol, glucagon), and immune mediators (thromboxane A_2, prostaglandin F_{2a}, prostaglandin E_2). Stress mediators cause proteolysis, glycogenolysis, gluconeogenesis, and lipolysis. As a result, critically ill patients have skeletal muscle breakdown, impaired amino acid transport into skeletal muscles, suppressed insulin-mediated

protein synthesis, depletion of body energy reserves and constitutive proteins, increased urea production, and peripheral insulin resistance. Protein catabolism is further exacerbated by metabolic acidosis that is typically seen in patients with acute kidney injury. The consequences of these metabolic derangements are manifested by loss of body energy reserves (glycogen, protein, and fat stores), negative nitrogen balance, hyperglycemia, and hypertriglyceridemia.[8, 9]

Acute kidney injury affects protein degradation and amino acid conversions due to impaired kidney metabolic functions. Serum amino acid concentrations such as phenylalanine, methionine, taurine, and cysteine are typically elevated, whereas serum valine and leucine concentrations are decreased in patients with acute kidney injury. Also, nonessential dispensable amino acids (e.g., tyrosine, arginine) become conditionally essential or indispensable, and phenylalanine conversion to tyrosine becomes inadequate in these patients.[10, 11] Further, critical illness and sepsis cause changes in the serum amino acid profile, with increased glutamine degradation and decreased serum phenylalanine concentrations.[12, 13]

Glutamine is the most abundant amino acid in skeletal muscles, is an essential fuel for enterocytes, and becomes conditionally essential or indispensable under metabolic stress.[14] Glutamine is also cleared in the effluent during CRRT. A study of critically ill adult patients with multiorgan dysfunction syndrome who were treated with CRRT and who received supplemental intravenous glutamine 0.5 g/kg over 20 hours for 2 days reported glutamine losses of 0.5–6.8 g/day through the hemodiafilter.[15] Glutamine clearance correlated with plasma glutamine concentrations and the effluent flow rate. The investigators suggested that glutamine be supplemented at 20 g/day in critically ill adult patients treated with CRRT. Glutamine is not a standard component of parenteral amino acid solutions, and the benefits of glutamine supplementation in critically ill patients remain debatable.[16]

Because energy requirements for critically ill patients vary with the level of metabolic stress, patient energy expenditure is best measured by using indirect calorimetry measurements. Although it is estimated that adult patients with acute kidney injury require total calories of 25–35 kcal/kg/day, indirect calorimetry provides a more accurate measurement of patient's energy expenditure while avoiding overfeeding.[6] A considerable amount of dextrose at about 35–45% of dialysate dextrose is absorbed during hemodiafiltration when dextrose-containing dialysate is used.[5] Dextrose contribution from dialysate should be included in the calculation of dextrose calories when designing a nutrition support regimen. Dextrose overfeeding results in hepatic steatosis and hyperglycemia.[17] Hyperglycemia enhances protein catabolism and increases patient morbidity and mortality.[18] Because dextrose uptake to the patient with dextrose-containing dialysate is much greater than dextrose loss, which is minor and of no clinical significance, use of dextrose-free dialysate and replacement fluid with CRRT is recommended.[19]

Assessment of Body Protein Status and Extent of Protein Catabolism

Methods to assess a patient's protein status include anthropometric measurements of the midarm circumference, biochemical measurements of serum visceral proteins, nitrogen balance studies, urea nitrogen appearance (UNA), and protein catabolic rate (PCR). Each of these methods has limited specificity or sensitivity in critical illness. Midarm circumference measurement to assess muscle mass is limited in the critically ill patient by fluid overload and patient positioning. Although serum visceral proteins (albumin, prealbumin, retinol-binding protein, transferrin) are clinically useful measurements of the patient's protein-calorie status, they are negative acute phase proteins and their serum concentrations are influenced by nonnutritional factors such as stress level, inflammation, and hydration status.[20]

Nitrogen Balance

Nitrogen balance describes the difference between body nitrogen gains and losses. Measuring nitrogen balance is based on the premise that nitrogen equilibrium is attained when protein supply is adequate to replace nitrogen loss through the urine, stools, wounds, desquamation of epithelial cells, and sweat. Most body nitrogen is contained in proteins, with nitrogen accounting for about 16% (assumption that protein is composed of 16% nitrogen [1/6.25 = 0.16]) of protein structure.[21] Nitrogen is released during protein catabolism and is mostly excreted in the urine in the form of urea. A positive nitrogen balance is a reflection that nitrogen intake exceeds nitrogen loss. A desired positive nitrogen balance is in the range of 4–6 g/day. However, protein catabolism and negative

nitrogen balance are unavoidable in the critically ill patient, and attaining a positive nitrogen balance is often difficult to achieve until the patient's metabolic stress resolves. In the stressed critically ill patient, nitrogen balance data may actually represent the degree of catabolism rather than the adequacy of protein intake. The time to achieve a zero nitrogen balance or nitrogen equilibrium varies among patients and from day to day depending on the type and degree of injury, comorbidities, metabolic stress, nutritional status, and nutritional intake. In the short term, nitrogen equilibrium in the nonanabolic, noncatabolic metabolically stable adult may be achieved in 5–7 days with adequate energy and protein intake. However, improved nitrogen balance has not necessarily been shown to be associated with enhanced muscle protein synthesis such as in critically ill patients receiving parenteral nutrition.[22]

In the nonstressed patient, urinary urea nitrogen (UUN) accounts for 80–90% of total urinary nitrogen. This estimate is not valid in critically ill patients and those with acute kidney injury, liver failure, or sepsis. Under these conditions, the percentage of nonurea urinary nitrogen components varies widely with the formation of nonurea nitrogen substances such as ammonia and uric acid.[23] Although measuring total urinary nitrogen is more accurate than UUN, laboratory measurement of total urinary nitrogen is extremely laborious. In addition, variations in nitrogen losses and the inability to accurately account for all nonurine nitrogen losses lead to problems in interpreting nitrogen balance studies. Because of limited laboratory resources, clinicians commonly rely on the measurement of UUN and use adjustment formulas to compensate for insensible nitrogen losses and nonurea nitrogen components. Equations used to measure nitrogen balance are as follows: nitrogen balance (g/day) = nitrogen intake (g/day) – nitrogen losses (g/day); nitrogen losses = UUN + nonurea urinary nitrogen (2 g) + fecal nitrogen (2 g).

Urea Nitrogen Appearance

A less laborious method used to measure the net rate of protein catabolism is UNA, which refers to urea in body fluids such as urine or output from fistulas and in dialysate. In patients treated with intermittent hemodialysis, UNA is calculated as follows[24]: UNA (g/day) = UUN (g/day) + dialysate urea nitrogen (g/day) + change in body urea nitrogen (g/day); change in body urea nitrogen (g/day) = $[(BUN_f - BUN_i) \times BW_i \times 0.6\ L/kg] + [(BW_f - BW_i) \times BUN_f \times 1\ L/kg]$, where BUN is blood urea nitrogen expressed in g/L and BW is body weight in kg. The i and f represent the initial (immediately after dialysis) and final (immediately before the second dialysis session) values for the period of measurement, respectively. The factor of 0.6 is an estimate of the fraction of adult body weight as water, and 1 is the fractional distribution of urea in the gained or lost weight.[25]

For patients treated with CRRT, urea is collected and measured in the ultrafiltrate and dialysate and added to the UUN and changes in body urea nitrogen. Nitrogen balance can then be calculated as follows: nitrogen balance = nitrogen intake – (UNA + other nitrogen losses). Other nitrogen losses in the range of 4–6 g/day include nitrogen loss during dialysis, in stools, through drainage, and other minor nitrogen losses through skin and sweat.

Protein Catabolic Rate

The PCR, also called protein equivalent of nitrogen appearance, is a measure of net protein degradation and is used to estimate protein intake. Under steady-state conditions, protein intake is equal or slightly greater than PCR. Because protein requirements are based on adjusted edema-free body cell mass, PCR is normalized to be expressed in grams of protein degraded daily divided by the dry body weight and is labeled as normalized PCR (nPCR). Limitations to nPCR include its wide variation in metabolically unstable patients, its rapid fluctuations with changes in protein intake, and its underestimation of protein intake when protein intake is high and overestimation of protein intake when protein intake is less than 1 g/kg/day.[20] The PCR is calculated as follows[26]: PCR (g/day) = UNA x 6.25.

The PCR closely correlates with protein intake only in the steady state of nitrogen equilibrium. Although PCR has been used in clinical studies of patients with acute kidney injury managed with CRRT, wide variations in PCR values have been reported, mainly in clinically unstable patients.[27–29] Repeat measurements of PCR are thus needed, as daily PCR, determined by single-day nitrogen balance studies, overestimates protein requirements in some patients and underestimates it in others.[30]

In a group of 10 adult patients with acute kidney injury managed with conventional 4-hour hemodialysis or 8-hour sustained low-efficiency

dialysis and who received fixed amino acid doses at 1.5 g/kg/day, mean PCR was 1.47 g/kg/day (range 0.97–1.8 g/kg/day).[31] Critically ill adult patients with acute kidney injury managed with CRRT who received an average amino acid intake of 1.4 g/kg/day had a mean PCR of 1.7 g/kg/day.[30] Another study of critically ill adult patients with acute kidney injury managed with CRRT reported a mean ± SD nPCR of 1.82 ± 0.95 g/kg/day.[27] This is in agreement with results from patients with acute kidney injury treated with different CRRT modalities who had a mean ± SD nPCR of 1.75 ± 0.82 (range 0.61–4.23 g/kg/day).[28] Higher PCR is expected in highly catabolic patients with severe burn injuries. Critically ill adult patients with acute kidney injury treated with CRRT who received amino acids at 1.8 + 0.4 g/kg/day had a higher PCR of 2.2 g/kg/day (range 1.2–4 g/kg/day).[29]

Amino Acid Requirements

Amino acids are nitrogenous compounds used as energy source and building blocks for proteins. Restriction of amino acid intake in patients with acute kidney injury is aimed at avoiding frequent dialysis caused by azotemia due to accumulation of nitrogenous waste. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommendation for amino acid intake in adult patients with chronic renal failure kidney disease before dialysis is 0.6–0.75 g/kg/day; in clinically stable patients undergoing maintenance hemodialysis, 1.2 g/kg/day; in patients receiving long-term peritoneal dialysis, 1.2–1.3 g/kg/day; and in acutely ill patients receiving maintenance hemodialysis, at least 1.2–1.3 g/kg/day.[20] For critically ill patients without renal or liver disease, higher amino acid doses of 1.5–2 g/kg/day are often used clinically.

In patients with acute kidney injury who are highly catabolic and severely malnourished, the American Society for Parenteral and Enteral Nutrition practice guidelines recommend amino acid intake at 1.5–1.8 g/kg/day.[32] In patients treated with CRRT, amino acid doses ranged from 1.2–2.5 g/kg/day. Because CRRT provides a superior control of azotemia compared with intermittent hemodialysis, higher amino acid intake is possible without worsening azotemia.[33]

Early developed specialized parenteral and enteral amino acid formulations that primarily provided essential amino acids were aimed at forcing the recycling of urea nitrogen for the synthesis of nonessential amino acids and to avoid worsening of azotemia. The rationale and efficacy of these products were questioned especially because of the inefficiency of urea recycling under stress[34, 35] and because some nonessential dispensable amino acids become conditionally essential or indispensable in patients with acute kidney injury.[36, 37] Therefore, the use of predominantly essential amino acid formulations has been abandoned, and standard products with a balanced mix of essential and nonessential amino acids are now clinically used. However, due to significant physiologic perturbations affecting amino acid balance in critically ill patients with acute kidney injury, the amino acid composition of standard parenteral amino acid formulations may not be optimal to normalize the plasma amino acid profile in these patients.

Role of Renal Replacement Therapy

Renal replacement therapy has supplanted intermittent hemodialysis as the preferred dialytic therapy in many ICUs.[38] With CRRT, the most critically ill patients can receive adequate renal supportive therapy, and it may confer a survival advantage over intermittent hemodialysis.[39] Because this therapy comes in many forms, an international consensus conference gave CRRT modalities standard definitions.[40] The two most commonly used forms of CRRT are continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD). The CVVH form provides convective solute clearance and consequently removes larger solutes than with the diffusive clearance of CVVHD. A hybrid of CVVH and CVVHD is continuous venovenous hemodiafiltration (CVVHDF) in which dialysate is used with additional fluid (ultrafiltrate) removed for additional convective clearance.

Solute removal with any modality is dependent on the amount of effluent (dialysate and/or ultrafiltrate) coming out of the filter and the ability of the solute to cross the hemodiafilter. The ability of a solute to cross the hemodiafilter membrane is calculated by measuring the solute concentration in the effluent and dividing by the simultaneous concentration of the blood entering into the hemodiafilter. The ratio of the effluent to blood concentration is called the sieving coefficient in CVVH or the equilibration coefficient in CVVHD and CVVHDF. If the coefficient is near 1, then the solute is readily cleared by CRRT, whereas a coefficient near zero reflects poor clearance.[41] Solute molecular weight for most nutrients is typically not an important determi-

nant in solute removal by CRRT. Contemporary hemodiafilters can effectively remove substances with molecular weights up to 5000 daltons. A more important determinant of a solute's sieving or equilibration coefficient is the degree of protein binding. Unbound solutes can usually cross the hemodiafilter membrane, but if they are bound to large proteins like albumin (molecular weight > 66,000 daltons), they will be unable to pass through the hemodiafilter. Multiplication of the solute's sieving coefficient (with CVVH) or equilibration coefficient (with CVVHD or CVVHDF) by the effluent rate yields the solute's clearance rate.[42] In addition to urea clearance, calculation of CRRT removal of drugs and nutritional components including amino acids is essential.[6, 43]

Factors Impacting Protein and Amino Acid Clearance Across Hemodiafilters

Small amounts of small proteins, peptides, and cytokines are eliminated in the effluent of renal replacement therapies.[44] High-flux hemodiafilters during a 4-hour conventional hemodialysis session cause insignificant dialysate albumin loss (< 0.5 g). However, superflux or protein-leaking membranes, although rarely used clinically, allow the passage of low-molecular-weight and protein-bound solutes with albumin losses of 2–6 g during a 4-hour hemodialysis session.[45] Minimal amounts of proteins of 1.6 g/day were lost in the effluent during CRRT when a polysulfone hemodiafilter membrane (mean ± SD effluent rate 1637 ± 694 ml/hr) was used. Significantly higher protein losses occurred with CVVH than with CVVHDF (2.2 vs 1 g/day, p=0.049).[46]

Amino acids have small molecular weights (average 140 daltons, range 75–215 daltons), with a sieving coefficient of 1, which makes their effluent losses with CRRT far greater than that for proteins. Amino acid effluent clearance depends on the duration of dialysis, dialysate flow rate, effluent rate, and types of hemodiafilter membranes.[44] During an intermittent hemodialysis session, mean ± SD amino acid dialysate losses were 12.6 ± 3.6 g during parenteral amino acid and glucose infusion.[47] Mean dialysate amino acid losses were 5.2 ± 0.6 g during intermittent hemodialysis, and 7.3 ± 1.8 g during high-flux hemodialysis.[48] During a 3-hour hemodialysis session using a polyacrylonitrile membrane, mean amino acid dialysate losses were about 6 g, twice the losses observed with the polysulfone membrane.[49] During a 4-hour hemodialysis session using polysulfone and polymethylmethacrylate membranes, mean± SD amino acid dialysate losses were 8 ± 2.8 g and 6.1 ± 1.5 g, respectively.[50] When intradialytic parenteral amino acids were administered, amino acid dialysate losses were 12 ± 2 g during a 4-hour hemodialysis session.[51] With slow diurnal hemodialysis (a hybrid of CRRT and intermittent hemodialysis with typical treatment duration of 6–12 hrs), mean ± SEM amino acid loss during a 10-hour dialysis session was 6.2 ± 0.6 g/day, equivalent to 16% of daily parenteral amino acid intake.[52]

Amino Acid Requirements with Continuous Renal Replacement Therapy

In a case report of a patient treated with CVVH, amino acid effluent losses correlated with the effluent rate. Doubling the ultrafiltration rate from 0.5 to 1 L/hour caused a greater than 3 times increase in mean amino acid ultrafiltrate losses, from 2.4 to 7.9 g/day, respectively.[53] Several clinical studies evaluated the effects of different CRRT modalities on amino acid clearance and requirements in critically ill patients with acute kidney injury (Table 1).[54–63]

A prospective, nonrandomized study evaluated the effects of CVVH on effluent amino acid clearance in eight critically ill adult patients with acute kidney injury.[54] Patients received parenteral nutrition that provided 1 L of amino acids with 1850 kcal of nonprotein calories. Study results showed that all amino acids were cleared in the ultrafiltrate. A positive correlation was shown between serum amino acid concentrations and ultrafiltrate amino acid losses. Patients with cardiogenic shock had a higher total ultrafiltrate amino acid loss of 7.4 g/day (11% of daily amino acid intake) compared with patients with sepsis, who had amino acid losses of 3.8 g/day (5.6% of daily amino acid intake). Patients with cardiogenic shock had higher serum amino acid concentrations than patients with sepsis, which may have resulted in higher amino acid clearance.

One prospective, randomized, crossover study evaluated the effects of CVVH and CVVHD on effluent amino acid clearance and nitrogen balance in six critically ill pediatric patients with acute kidney injury.[55] Patients received parenteral nutrition that provided amino acids at 1.5 g/kg/day with a caloric intake at 120–130% of measured resting energy expenditure. Study results showed a 30–40% higher amino acid clearance (except for glutamine) with CVVH compared with

Table 1. Clinical Studies of Amino Acid Requirements in Critically Ill Patients with Acute Kidney Injury Treated with Continuous Renal Replacement Therapy

Study Design	Patient Population	CRRT Modality and Effluent Rate	Amino Acid and Caloric Intake	Primary End Points
Prospective, nonrandomized[54]	Adults (n=8)	CVVH, high-flux; 1 L/hr	Parenteral nutrition: amino acids 1 L/day, nonprotein calories 1850 kcal/day	Amino acid losses across hemodiafilter
Prospective, randomized, crossover[55]	Children (n=6)	CVVH, CVVHD; 2 L/hr	Parenteral nutrition: amino acids 1.5 g/kg/day, calories 1.2–1.3 x resting energy expenditure	Amino acid losses across hemodiafilter, nitrogen balance
Prospective, nonrandomized[56]	Adults (n=6)	CAVHD; 1 or 2 L/hr	Parenteral nutrition: amino acids 56–112 g/day, nonprotein calories 2000–2400 kcal/day	Amino acid losses across hemodiafilter
Prospective, nonrandomized, unblinded[57]	Adults: treatment group (n=17), control group with normal renal function (n=15)	CAVHD, CVVHD; 0.9 or 1.8 L/hr	Parenteral nutrition: Treatment group: amino acids 2.19 ± 0.48 g/kg/day, nonprotein calories 3077 ± 1018 kcal/day Control group: amino acids 2.24 ± 0.36 g/kg/day, nonprotein calories 3015 ± 753 kcal/day	Amino acid losses across hemodiafilter
Prospective, cohort, interventional[58]	Adults with MODS and APACHE II score of 28.2 (n=9)	CAVHD; 1 or 2 L/hr	Parenteral nutrition: amino acids 1.25–1.87 g/kg/day, nonprotein calories 1850 kcal/day	Nitrogen balance
Prospective, nonrandomized, noninterventional[59]	Adults with APACHE II score of 25 ± 9 (n=40)	CVVH; 1 L/hr	No nutrition (n=6) Enteral and/or parenteral nutrition (n=34): amino acids 1 ± 0.4 (range 0.3–1.9) g/kg/day, nonprotein calories 28 ± 9 (range 13–53) kcal/kg/day	Nitrogen balance, protein catabolism, amino acids < 1 vs ≥ 1 g/kg/day
Prospective, interventional[60]	Adults with APACHE II score of 20.5 ± 7 (n=11); 3 had multiple trauma, 2 had extensive burns	CVVHD; 2 L/hr	Parenteral nutrition: amino acids 1 g/kg/day increased by 0.25 g/kg/day to 2.5 g/kg/day, nonprotein calories 2585 kcal/day	Effects of amino acid intake on serum amino acid concentrations, amino acid balance, amino acid losses across hemodiafilter
Prospective, interventional[61]	Adults with APACHE II score of 26 ± 8: treatment group (n=40), control group (n=10)	CVVHD; 2 L/hr	Parenteral and/or enteral nutrition: Treatment group: amino acids 1.5 g/kg/day x 2 days, then 2 g/kg/day x 2 days, then 2.5 g/kg/day x 2 days Control group: amino acids 2 g/kg/day, calories 2101 ± 410 kcal/day	Nitrogen balance, survival

Table 1. (continued)

Results
All amino acids cleared in ultrafiltrate
Amino acid losses correlate with serum amino acid concentrations and clinical condition
Cardiogenic shock: amino acid loss 7.4 g/day (11% of amino acid intake)
Sepsis: amino acid loss 3.8 g/day (5.6% of amino acid intake)
Serum amino acid concentrations within normal ranges except for high serum phenylalanine and low serum glutamine concentrations in both groups of cardiogenic shock and sepsis
For all amino acids (except glutamine): 30–40% greater losses with CVVH vs CVVHD
No significant difference in amino acid losses as percentage of intake with CVVH (12%) vs CVVHD (11%)
Negative nitrogen balance, but no significantly different effect on nitrogen balance between CVVH and CVVHD (-3.68 ± 3.1 vs -0.44 ± 1.7 g/day/1.73 m^2)
Amino acid losses as percentage of intake were higher at effluent rate of 2 L/hr (12.1 ± 2.2%) vs 1 L/hr (8.9 ± 1.2%)
Higher amino acid losses at effluent rate of 1.8 L/hr (7.9 ± 2.6 g/12 hrs) vs 0.9 L/hr (5.7 ± 1.7 g/12 hrs, p<0.0001)
Amino acid losses as percentage of intake higher at effluent rate of 1.8 L/hr (6.4 ± 2.5%) vs 0.9 L/hr (4.8 ± 1.5%, p<0.0001)
No significant difference in amino acid losses between CAVHD and CVVHD
Amino acid losses correlated with serum amino acid concentrations but not with amino acid intake
Effluent glutamine loss (2 g/day) with CVVHD but not resulting in glutamine deficiency
Effluent nitrogen losses (24.1 g/day) exceeded intake (20.5 g/day)
Negative nitrogen balance (-3.6 g/day)
Normalized protein catabolic rate 1.4 ± 0.5 g/kg/day (0.6–2.5 g/kg/day)
Higher amino acid intake resulted in less negative nitrogen balance (-3.5 ± 4.2 g/day) vs lower amino acid intake (-8.4 ± 4.9 g/day, p=0.004)
Serum amino acid concentrations normalized only with amino acid intake at 2.5 g/kg/day
Correlation between amino acid intake and losses (except tyrosine)
Amino acid losses as percentage of intake at 17% (range 13–24%)
Nitrogen balance positively related to nitrogen intake (p=0.0075)
Nitrogen balance more likely achieved with amino acid intake > 2 g/kg/day (p=0.0001)
Each nitrogen balance increase by 1 g/day increased patient survival probability by 21%

CVVHD. No significant difference was noted between CVVH and CVVHD on calculated amino acid loss (mean ± SEM 12.5 ± 1.3 and 11.6 ± 1.8 g/day/1.73 m^2, respectively). Mean nitrogen balance was negative with both CVVH and CVVHD (-3.68 ± 3.1 and -0.44 ± 1.7 g /day/1.73 m^2, respectively). Amino acid loss averaged 12% and 11% of the daily amino acid infusion with CVVH and CVVHD, respectively. The investigators speculated that higher amino acid intake is needed in these patients to achieve a positive nitrogen balance. Because pediatric patients have higher amino acid requirements than that of adult patients, data derived from this study in children may not necessarily apply to adults.

A correlation between dialysate flow rate and effluent amino acid loss was reported with continuous arteriovenous hemodialysis (CAVHD) and CVVHD.[56, 57] A prospective, nonrandomized study evaluated effluent amino acid losses in six critically ill adult patients treated with CAVHD.[56] Daily parenteral nutrition provided amino acids at 56 g in 1 patient, 87 g in 2 patients, and 112 g in 3 patients. Nonprotein calories ranged from 2000–2400 kcal/day. Study results showed a mean 36% higher effluent amino acid loss as a percentage of amino acid intake at a dialysate flow rate of 2 L/hour compared with 1 L/hour (12.1 ± 2.2% vs 8.9 ± 1.2%). This translates to daily amino acids losses of 6.7, 10, and 13.6 g with the dialysate flow rate of 2 L/hr and 4.9, 7.7, and 10 g for the dialysate flow rate of 1 L/hr of the respective daily amino acid intake of 56, 87, and 112 g.

Similarly, a prospective, nonrandomized, nonblinded study of 17 adult trauma patients with acute kidney injury evaluated the effects of CAVHD or CVVHD on amino acid clearance compared with a control group of similar patients with normal renal function.[57] Amino acid intake was similar at mean ± SD 2.19 ± 0.48 and 2.24 ± 0.36 g/kg/day in the study and control groups, respectively. Caloric intake was also similar, with nonprotein calories at 3077 ± 1018 and 3015 ± 753 kcal/day in the study and control groups, respectively. Study results showed no significant difference in amino acid losses between CAVHD and CVVHD. Amino acid losses were significantly higher at a dialysate flow rate of 1.8 L/hour compared with a dialysate rate of 0.9 L/hour (7.9 ± 2.6 and 5.7 ± 1.7 g/12 hrs, respectively, p<0.0001), equivalent to daily amino acids losses at about 16 and 11 g, respectively. Predictors of effluent amino acid losses were serum amino acid concentrations during the

Table 1. Clinical Studies of Amino Acid Requirements in Critically Ill Patients with Acute Kidney Injury Treated with Continuous Renal Replacement Therapy (continued)

Study Design	Patient Population	CRRT Modality and Effluent Rate	Amino Acid and Caloric Intake	Primary End Points
Prospective, nonrandomized, cohort[62]	Adults (surgical or medical): cohort 1 (n=24), cohort 2 (n=16)	CVVHD, CAVHD; 1 or 2 L/hr	Parenteral nutrition: Cohort 1: amino acids 1.2 (range 0.41–2.4) g/kg/day Cohort 2: amino acids 2.5 g/kg/day; nonprotein calories 30–35 kcal/kg/day	Nitrogen balance, survival
Prospective, nonrandomized, cohort[63]	Adults with MODS (n=7)	CVVHDF; 1 or 2 L/hr	Parenteral nutrition: amino acids 2.5 g/kg/day, nonprotein calories 35 kcal/kg/day	Amino acid losses across hemodiafilter, nitrogen balance

Data are mean, mean ± SD, or range.
CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CAVHD = continuous arteriovenous hemodialysis; APACHE = Acute Physiology and Chronic Health Evaluation; MODS = multiorgan dysfunction syndrome; CVVHDF = continuous venovenous hemodiafiltration.

study period, effluent volume, and the efficiency of dialysis. There was a higher proportion of amino acid loss as a percentage of amino acid intake with a dialysate rate of 1.8 L/hour compared with 0.9 L/hour (6.4 ± 2.5% vs 4.8 ± 1.5%, p<0.0001). However, amino acid intake was not predictive of hemodiafilter amino acid losses. A study limitation is the choice of a control group with normal renal function leading to a baseline mismatch between the control and treatment groups.

The effect of CAVHD on nitrogen balance was evaluated in nine critically ill adult patients with acute kidney injury.[58] Patients received amino acids at 1.25–1.87 g/kg/day with 1850 kcal/day of nonprotein calories in their parenteral nutrition. Study results showed a significant average effluent loss of nitrogen (24.1 g/day) that exceeded the average nitrogen intake in parenteral nutrition (20.5 g/day). This resulted in an average negative nitrogen balance of -3.6 g/day or -0.045 g/kg/day. The investigators suggested that increasing amino acid intake may achieve a positive nitrogen balance.

A prospective, nonrandomized study evaluated the variables that may affect nitrogen balance and protein catabolism in 40 consecutive critically ill adult patients with acute kidney injury managed with CVVH.[59] Mean amino acid intake in the 34 patients who received parenteral nutrition and/or enteral nutrition was mean ± SD 1 ± 0.4 g/kg/day (range 0.3–1.9 g/kg/day) with mean total nonprotein calories of 28 ± 9 kcal/kg/day (range 13–53 kcal/kg/day). Study results showed for all patients a mean PCR of 1.4 ± 0.5 g/kg/day (range 0.6–2.5 g/kg/day). Patients who received nutrition support were evaluated based on amino acid intake of less than 1 g/kg/day (0.7 ± 0.2 g/kg/day) and greater than or equal to 1 g/kg/day (1.3 ± 0.2 g/kg/day). A significantly less negative nitrogen balance was noted in patients who received amino acids 1 g/kg/day or more compared with those who received less than 1 g/kg/day (-3.5 ± 4.2 vs -8.4 ± 4.9 g/day, p=0.004). Positive nitrogen balance was achieved in 29.4% of patients who received amino acids 1 g/kg/day or more, whereas none of the patients in the less than 1 g/kg/day group achieved positive nitrogen balance. The rate of mortality was not significantly different between the two groups. A multivariate regression analysis of the different caloric and amino acid intake showed that higher amino acid intake of 1.5 g/kg/day or more or even more than 2 g/kg/day can achieve positive nitrogen balance that can be further improved with nonprotein caloric intake of no more than 30–35 kcal/kg/day. Of interest, increasing caloric intake in patients who received amino acids of more than 1.5 g/kg/day was associated with increased protein catabolism. At an amino acid intake of more than 2 g/kg/day, lower caloric intake was associated with improved nitrogen balance. To optimize nitrogen retention, study investigators recommended that critically ill patients treated with CVVH should receive amino acids at 1.5–1.8 g/kg/day with caloric intake of 25–35 kcal/kg/day.

Amino acids at doses of 2 g/kg/day or more were associated with a greater chance of normalizing

Table 1. (continued)

Results
High amino acid intake resulted in less negative nitrogen balance (-1.92 g/day) vs low amino acid intake (-5.5 g/day, p=0.176)
Effluent daily amino acid losses similar between groups
Survival similar between groups
High amino acid intake caused higher plasma urea concentrations, requiring more aggressive dialysis
Median amino acid losses of 12 g/day (5–21% of daily amino acid intake)
Median nitrogen balance -1.8 g/day (range -21 to +17.9 g/day)
Positive nitrogen balance 35% of time
No effect on improvement in patient outcome

serum amino acid concentrations and improving nitrogen balance. A prospective interventional study evaluated the effects of different levels of amino acid intake on serum amino acid concentrations, amino acid balance, and amino acid losses in 11 adult critically ill patients with acute kidney injury treated with CVVHD.[60] All patients received parenteral nutrition that provided amino acids initially at 1 g/kg/day then increased at 24-hour intervals by 0.25 g/kg/day to a maximum of 2.5 g/kg/day. Mean nonprotein caloric intake was 2585 kcal/day (35 kcal/kg/day). Study results showed that, with amino acid dosing at less than 2.5 g/kg/day, 14–57% of serum amino acid concentrations were below normal range. Although keeping caloric intake constant, amino acid balance became increasingly positive as amino acid intake increased from 1 to 2.5 g/kg/day (p=0.0001). Serum amino acid concentrations did not normalize until amino acid intake reached 2.5 g/kg/day. Overall, amino acid losses through the hemodiafilter were 17% (13–24%) of amino acid intake. Blood urea concentrations increased with higher amino acid intake but remained at acceptable average concentrations of less than 61.6 mg/dl. The investigators recommended that adult patients treated with CRRT receive amino acids at 2.5 g/kg/day to correct amino acid deficiencies and improve nitrogen retention. However, combining data from a diverse patient population with various clinical conditions may preclude generalization of results. Of the 11 patients, 3 had multiple trauma and 2 others had extensive burns. Patients with severe trauma or burn injuries normally have higher amino acid requirements to counteract hypercatabolism and promote wound healing. Also, significant protein losses from draining wounds and exfoliating burns could not be measured and could have affected the accuracy of nitrogen balance studies. Further, normalization of serum amino acid concentrations in correlation with amino acid intake should be interpreted with caution. Serum amino acid concentrations depend not only on amino acid intake, but also on endogenous breakdown and production as a function of stress level and degree of injury.

The same investigators further reported in a prospective interventional study the effects of high amino acid intake on nitrogen balance and patient outcomes in 50 sequential adult critically ill patients with acute kidney injury treated with CVVHD.[61] The treatment group included 40 patients who received amino acids at 1.5 g /kg/day for 2 days, then 2 g/kg/day for the next 2 days, and then 2.5 g/kg/day for the last 2 days. Ten patients in the control group received a fixed amino acid dosage of 2 g/kg/day to eliminate time-effect on nitrogen balance. Patients received enteral nutrition and/or parenteral nutrition based on tolerance with a caloric intake of mean ± SD 2101 ± 410 kcal/day. Study results showed that nitrogen balance was positively related to amino acid intake (p=0.0075). Attaining positive nitrogen balance was more likely with amino acid intake greater than 2 g/kg/day (p=0.0001). The probability of survival increased by 21% for every 1-g/day increase in nitrogen balance. However, despite the association of nitrogen balance to patient morbidity and mortality, the multivariate analysis, after adjusting for age, sex, diagnosis category, and Acute Physiology and Chronic Health Evaluation (APACHE) II score, showed no significant direct relationship between amino acid intake and patient outcomes.

A prospective, nonrandomized, cohort study of 40 adult medical and surgical critically ill patients with acute kidney injury treated with CAVHD or CVVHD compared the metabolic and clinical effects of two levels of amino acid intake.[62] One group of 24 patients received parenteral amino acids at an average of 1.2 g/kg/day (range 0.41–2.4 g/kg/day) and a second group of 16 patients received fixed amino acid doses at 2.5 g/kg/day. Parenteral nutrition provided patients in both groups with nonprotein calories at 30–35 kcal/kg/day. In contrast to previous results, study results showed that nitrogen loss was greater in patients who received higher amino acid intake, but effluent amino acid losses were similar in both groups. Patients in the high amino acid intake group had a less negative mean nitrogen

balance compared with the lower intake group, although the difference did not achieve statistical significance (-1.92 vs -5.5 g/day, p=0.176). Also, despite greater nitrogen loss, the high amino acid intake group had a higher percentage of treatment days in positive nitrogen balance compared with the lower amino acid intake group (53.6% vs 36.7%, p<0.05). However, high amino acid intake was associated with a higher mean plasma urea concentration compared with lower amino acid intake (26.6 vs 18 mmol/L, p<0.0001) and thus required more aggressive dialysis to control azotemia. No significant difference in survival rates was shown between the two groups. Although the investigators speculated that amino acid intake of greater than 3 g/kg/day may be needed to reach close-to-neutral nitrogen balance, they proposed an amino acid intake at 1.8–2 g/kg/day as an optimal compromise to improve nitrogen balance and avoid worsening of azotemia.

The same investigators later evaluated the effects of high parenteral amino acid doses at 2.5 g/kg/day on nitrogen balance in seven adult critically ill patients with acute kidney injury who had multiorgan dysfunction syndrome treated with CVVHDF.[63] All patients received parenteral nutrition that provided nonprotein calories at 35 kcal/kg/day. Study results showed median amino acid losses of 12 g/day (5–21% of daily amino acid intake). Median nitrogen balance was slightly negative at -1.8 g/day (range -21 to +17.9 g/day) with a positive nitrogen balance achieved in 7 of the 20 study days. Plasma urea concentrations were maintained at a median 75.4 mg/dl. The investigators concluded that amino acid intake at 2.5 g/kg/day in adult critically ill patients with acute kidney injury treated with CRRT can provide near-neutral to positive amino acid balance while maintaining azotemic control.

Impact of Nutritional Status and Amino Acid Intake on Patient Outcomes

Severe malnutrition occurs in up to 42% of patients with acute kidney injury. Severely malnourished patients have a significantly increased in-hospital length of stay, increased risk for comorbidities (sepsis, septic shock, hemorrhage, intestinal occlusion, cardiac dysrhythmia, cardiogenic shock, acute respiratory failure), and increased in-hospital mortality.[64] Therefore, optimizing nutritional status in these patients is important to improve patient outcome.

Protein catabolism results in malnutrition and predisposes patients to increased morbidity and mortality.[65, 66] Although attaining a positive nitrogen balance may not always be possible in critically ill patients, optimizing protein and caloric intake in patients managed with CRRT will improve nitrogen balance. In clinical studies, there was no improvement in patient survival and clinical outcomes despite increasing amino acid intake and improving nitrogen balance.[59, 62, 63] One of the limitations addressed by the investigators was that studies were too small to detect a difference.[63] Also, there was no association between positive nitrogen balance and patient number of days receiving ventilation, or hospital or ICU length of stay.[61] Results of nitrogen balance studies in critically ill patients should be interpreted with caution due to the heterogeneity of the critically ill population; the variability in nitrogen intake, metabolism, and losses; and the limitations of traditional nitrogen balance equations. Although nitrogen balance studies provide an idea about nitrogen retention, they do not provide information about amino acid pharmacokinetics or whole-body protein turnover including protein synthesis and breakdown.[67]

Amino acid intake during dialysis increases net muscle protein synthesis but does not decrease protein breakdown.[68] In patients receiving maintenance intermittent hemodialysis, amino acid losses in the dialysate lower serum amino acid concentrations, but intracellular amino acid concentrations remain unchanged probably due to enhanced intracellular amino acid transport.[69] Increasing amino acid intake increases serum amino acid concentrations, and a linear correlation exists between plasma amino acid concentrations and stimulation of muscle protein synthesis. However, the maximal capacity for stimulation of muscle protein synthesis is reached with only little increases in protein synthesis at serum amino acid concentrations greater than 2.5 times the normal postabsorptive serum amino acid concentrations. Therefore, amino acid intake in amounts that exceed muscle protein synthetic capacity may alternatively be oxidized or used for ureagenesis and gluconeogenesis.[70, 71]

Little is known about the safety and physiologic effects of increasing individual amino acid intake in patients with acute kidney injury. In experimental models of acute kidney injury, amino acids such as glycine, alanine, and taurine showed potential renal protective effects by limiting renal tubular injury, whereas methionine, serine, and lysine may be nephrotoxic.[26, 72–75] The role of

arginine in critical illness and in immunocompromised patients is widely debated. Arginine may have immunomodulatory effects, is essential for lymphocyte function, and is a precursor of nitric oxide. Although nitric oxide may have positive antiinflammatory effects and improve microvascular and renal blood flow, it may mediate tissue damage in patients with sepsis.[76–80] It is debatable whether nitric oxide is nephrotoxic or has renal protective effects. In animal studies of rats with induced ischemic acute kidney injury, increased L-arginine transport and nitric oxide production worsened renal tubular injury during the reperfusion period through the formation of peroxynitrite.[80] In contrast, nitric oxide release by L-arginine was shown to improve renal hemodynamics in ischemic acute kidney injury in rats and partially reduce kidney dysfunction induced by cyclosporine.[81, 82]

Conclusion

Protein catabolism is unavoidable in critically ill patients and results in negative nitrogen balance. Caloric and protein intake both affect nitrogen retention. In clinical studies of critically ill patients with acute kidney injury treated with CRRT, amino acid losses ranged widely from 5–21% of amino acid intake. Differences in patient populations, sample sizes, study outcomes, dialytic modalities, effluent rates, and hemodiafilter properties may have caused this wide variation. At the clinically common effluent rate of 2 L/hour, it is reasonable to estimate amino acid losses at about 10–15% of amino acid intake. However, because amino acid clearance through CRRT correlates with serum amino acid concentrations rather than amino acid intake, it may be more appropriate to quantify amino acid losses in gram amounts rather than in percentage of amino acid intake. For an effluent rate of 2 L/hour, amino acid losses ranged from 5–15 g/day with the higher losses corresponding with the high amino acid intake. Amino acid losses of 15 g/day translate to an equivalent amino acid loss of 0.2 g/kg/day for an adult weighing 75 kg. Normally, critically ill adult patients receive amino acids at 1.5–2 g/kg/day. Practically, adding amino acids at 0.2 g/kg/day to compensate for effluent losses would amount to amino acid doses of 1.7–2.2 g/kg/day for critically ill adult patients treated with CRRT.

In comparison, clinical studies reported improved nitrogen balance with high amino acid intake at 2.5 g/kg/day. However, the correlation between improved nitrogen balance and patient outcome remains unknown. Amino acid intake should be tailored to the specific patient needs. Patients with hepatic encephalopathy are intolerant to high protein intake and require lower amino acid dosing. Patients with trauma, burns, and sepsis are hypercatabolic and benefit from higher amino acid intake. Data from large, randomized, controlled studies are needed to define the optimal amino acid dosing regimen in patients managed with CRRT, as well as the safety of high amino acid intake and its effects on patient morbidity and survival.

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