Invited Review

Metabolic and Nutritional Aspects of Acute Renal Failure in Critically Ill Patients Requiring Continuous Renal Replacement Therapy

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ABSTRACT: Acute renal failure (ARF) is rarely an isolated process but is often a complication of underlying conditions such as sepsis, trauma, and multiple-organ failure in critically ill patients. As such, concomitant clinical conditions significantly affect patient outcome. Poor nutritional status is a major factor in increasing patients' morbidity and mortality. Malnutrition in ARF patients is caused by hypercatabolism and hypermetabolism that parallel the severity of illness. When dialytic intervention is indicated, continuous renal replacement therapy (CRRT) is a commonly used alternative to intermittent hemodialysis because it is well tolerated by hemodynamically unstable patients. This paper reviews the metabolic and nutritional alterations associated with ARF and provides recommendations regarding the nutritional, fluid, electrolyte, micronutrient, and acid-base management of these patients. The basic principles of CRRT are addressed, along with their nutritional implications in critically ill patients. A patient case is presented to illustrate the clinical application of topics covered within the paper.

Acute renal failure (ARF) is a common complication experienced by critically ill patients. About 10%–30% of patients in the intensive care unit (ICU) develop ARF, and 5%–10% of these patients are treated with continuous renal replacement therapy (CRRT).[1–4] Morbidity and mortality rates in critically ill patients with ARF remain high and range

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between 40% and 80%.[1–4] This may reflect the fact that patients in the ICU are now older, sicker, and have more underlying comorbidities than in the past.[5] The goals of therapy for ARF are to limit further renal injury; support the patient until kidney function recovers; correct azotemia and the fluid, electrolyte, and acid-base abnormalities; prevent systemic complications; and permit nutrition and other supportive therapies to be provided with minimal limitation.[1,6–8]

ARF is characterized by the rapid decline in renal function. As a result, excretion of nitrogenous waste is compromised and fluid and electrolyte balance cannot be maintained.[9] Clinically, ARF is defined as an acute elevation of the serum creatinine level from baseline.[9] Complete renal failure is evident when the serum creatinine level rises by at least 0.5 mg/dL per day and urinary output falls below 400 mL per day.[9] ARF can be stratified, in terms of diagnosis and treatment, into 3 categories: prerenal, intrinsic, and postrenal.[9] Prerenal ARF is the result of diminished blood flow to the kidneys.[9] Intrinsic ARF develops from damage to the renal parenchyma, and postrenal ARF is caused by an obstruction in the urinary tract.[9]

Malnutrition is common in patients with ARF and is a likely contributor to increased morbidity and mortality.[2,5] Although providing nutrition support is important in critically ill catabolic patients, the effects of nutrition support on reducing the morbidity and mortality of ARF patients is yet to be proven.[7] The purpose of this paper is to review the metabolic and nutritional alterations associated with ARF, discuss nutrition support of ARF patients, and address the nutritional implications of various CRRT modalities.

Metabolic and Nutritional Aspects of ARF

Metabolic implications of ARF include hypercatabolism, fluid and electrolyte abnormalities, and metabolic acidosis. The metabolic response to stress is associated with increased production of stress

mediators, including the counterregulatory hormones (catecholamines, cortisol, glucagon, growth hormone), cytokines (interleukin-1, interleukin-6, tumor necrosis factor-α), and other immune mediators (thromboxane A2, prostaglandin F2a, prostaglandin E2). These stress mediators enhance proteolysis, glycogenolysis, gluconeogenesis, and lipolysis. The end results are accelerated skeletal muscle catabolism, impaired amino acid transport into skeletal muscles, reduced insulin-mediated protein synthesis, increased urea production, and peripheral insulin resistance. These effects, in turn, lead to a negative nitrogen balance, hyperglycemia, and hypertriglyceridemia.[1–2,6,10]

The kidneys play a major role in regulating fluid, electrolyte, and acid-base balance. In ARF, significant imbalances in fluid, electrolytes, and acid-base may occur. The magnitude of these imbalances varies with the degree of renal impairment. The severity of renal injury and its effects on glomerular filtration will dictate the extent of complications. Adaptive mechanisms usually fail to correct these disturbances because of the rapid nature of ARF. In oliguric (urine output 100–400 mL/day) and anuric (urine output <100 mL/day) renal failure, significant fluid, electrolyte, and acid-base disturbances occur compared with nonoliguric (urine output >400 mL/day) renal failure. Because ARF is rarely an isolated entity but is often a complication of underlying conditions, coexisting diseases also contribute to complications.

Fluids

Water Physiology

Water is approximately 60% of the adult body mass. The intracellular fluid consists of fluids within the cells and composes about two-thirds of total body water. The extracellular fluid composes about one-third of total body water and consists mainly of plasma and interstitial fluid. Because of the generous perfusion of the kidneys, with the renal artery carrying about 20% of the cardiac output, ARF results in significant alteration in water filtration.

Fluid Imbalance

Oliguric and anuric ARF result in reduced renal water excretion, leading to total body fluid overload. Reduced urine output causes expansion of the extracellular fluid volume and accumulation of a plasma ultrafiltrate in the interstitial space or edema. Insensible water losses continue to occur from the gastrointestinal tract and skin and as a result of metabolic activities. In oliguric ARF patients, fluid intake is typically restricted to 500–1000 mL/day. In nonoliguric ARF patients, urine volume is high, negating the need for fluid restrictions. Patients recovering from anuric renal failure or acute tubular necrosis may have high urine water losses caused by decreased tubular responsiveness to the effects of

antidiuretic hormone (ADH). Critically ill catabolic patients have excess renal free water loss as a result of the osmotic diuretic effects of increased urea formation.[11]

Electrolytes

Sodium Homeostasis

Sodium is the major extracellular cation. It is the most osmotically active substance that is responsible for water homeostasis and the regulation of the extracellular fluid volume. Sodium exchanges occur along the kidney tubule *via* different transport mechanisms. Small variations in plasma sodium levels cause changes in the release of ADH to regulate water balance.[12]

Sodium Imbalances

Changes in serum sodium levels commonly reflect changes in water balance. In edematous patients with fluid overload, hyponatremia may indicate a dilutional effect. However, total body sodium may be increased, decreased, or normal, depending on the etiology of the hyponatremia.[13] A sudden reduction in the glomerular filtration rate in oliguric or anuric ARF results in sodium retention. However, renal sodium excretion is high, and sodium restriction is of a lesser issue in the nonoliguric patient. Excessive sodium intake in oliguric ARF patients increases fluid retention and is common cause of diuretic failure. As such, restriction of sodium intake in ARF patients is necessary, especially in the case of fluid retention. However, infusion of normal saline solutions may be necessary when volume expansion and increasing renal perfusion are indicated. Calculation of the fractional excretion of sodium helps differentiate acute intrinsic renal failure from prerenal azotemia. A fractional excretion of sodium >1%–1.5% suggests acute renal tubular injury. A fractional excretion of sodium <1% in oliguric patients is characteristic of prerenal azotemia or functional ARF. In either case, renal sodium conservation is increased. However, there are cases of acute intrinsic renal failure with a low fractional excretion of sodium <1% such as ARF caused by rhabdomyolysis, interstitial nephritis, and contrast-dye nephrotoxicity. Caution should also be used in the interpretation of the fractional excretion of sodium in patients treated with diuretics where urinary sodium excretion is increased.[14] It is thus crucial to interpret urinary sodium values in the context of the patient's medical history and clinical presentation.

Potassium Homeostasis

Potassium is the most abundant intracellular cation. About 90% of potassium is intracellular, 2% is in the extracellular fluid, and the remaining potassium is in the cartilage and bones. Most potas-

sium is normally excreted *via* the kidneys. Potassium is freely filtered at the glomerulus, and about 85% of potassium is reabsorbed in the proximal tubule and loop of Henle. The cortical collecting duct secretes and reabsorbs potassium. In case of excess potassium intake that exceeds the kidney's excretion ability, the intracellular space temporarily stores potassium until renal mechanisms can excrete the potassium load. The H^+-K^+-ATPase pump plays a major role in potassium handling in the kidneys, and the Na^+-K^+-ATPase pump is the rate-limiting step for potassium entry into the cells.[15]

Potassium Imbalances

Because potassium is mainly excreted *via* the kidneys, decreased glomerular filtration rate in ARF patients results in hyperkalemia. Nonoliguric ARF is unlikely to cause hyperkalemia, except in the case of tubular defects or obstructive nephropathy. In oliguric ARF, total urinary potassium excretion may be <20 mEq/day. Other causes of hyperkalemia in ARF patients may include cell turnover, intravascular hemolysis, acidosis, and the transfusion of hemolyzed red blood cells. Cell turnover is typical of catabolic ARF causing endogenous release of potassium. Metabolic acidosis increases extracellular potassium distribution that further increases serum potassium levels.

Hyperkalemia can be extremely dangerous, causing life-threatening arrhythmias. Serum potassium levels >6.5 mEq/L may result in severe cardiac (bradycardia, arrhythmias with peaking T waves, ventricular fibrillation) and neuromuscular (paresthesias, weakness) complications. These complications can be further aggravated if hypocalcemia coexists. Severely hyperkalemic or symptomatic patients should be treated with IV calcium gluconate or calcium chloride injections to antagonize cardiac conduction abnormalities. Any exogenous sources of potassium can rapidly increase serum potassium levels in oliguric or anuric ARF patients.[15] Therefore, potassium intake should be eliminated in anuric patients and restricted to <20–40 mEq/day in oliguric patients.

In nondialyzed patients with hyperkalemia, pharmacologic interventions are needed to correct the hyperkalemia by increasing intracellular potassium distribution or increasing its elimination. Increased intracellular potassium distribution is achieved with the administration of sodium bicarbonate and insulin. Concomitant dextrose infusion ($D_{10}W$ or $D_{50}W$) increases endogenous insulin secretion that will further enhance intracellular potassium redistribution and also avoids the possible hypoglycemia induced by exogenous insulin administration. However, hyperglycemia should be avoided because it increases extracellular potassium redistribution and worsens hyperkalemia. Increased potassium excretion can be achieved by the administration of loop diuretics in diuretic-responsive patients. The administration or sodium polystyrene sulfonate orally or rectally binds intestinal potassium and reduces potassium absorption. Serum potassium levels should be followed closely, and potassium supplements should only be administered as needed to correct the hypokalemia when it occurs. IV potassium is usually administered at infusion rates of 10–20 mEq/h.[16,17]

Phosphorus Homeostasis

About 85% of phosphorus is in the skeleton, 14% in soft tissues, and only 1% in the extracellular compartment. Phosphorus is the major intracellular anion, mostly found in the forms of esters, adenosine diphosphate, adenosine triphosphate, 2,3-diphosphoglycerate, and fructose 1,6-diphosphate. Physiologic regulators of phosphorus homeostasis involve mainly the parathyroid hormone and vitamin D. The kidneys are the major route of phosphorus excretion by filtration mechanisms, with about 80%–90% of phosphorus reabsorbed at the kidney tubule.[12]

Phosphorus Imbalances

Hyperphosphatemia is a common complication of oliguric and anuric ARF. A less significant degree of hyperphosphatemia occurs in nonoliguric ARF patients. Hyperphosphatemia is the result of decreased renal phosphorus excretion and increased endogenous release of phosphates as a result of cell lysis during hypercatabolism. Clinical manifestations of severe hyperphosphatemia are primarily the result of calcium-phosphate precipitation. Metastatic calcification in joints and soft tissues may occur in renal-failure patients when the product of serum calcium and phosphorus levels exceeds 60–70 mg/dL. Severe hyperphosphatemia may also cause hypocalcemia and subsequent tetany. The treatment of hyperphosphatemia consists of eliminating all sources of phosphorus, administration of oral phosphate binders, or treatment with dialysis if necessary. IV calcium should not be used to treat hyperphosphatemia as it may precipitate metastatic calcification, hypotension, and renal failure. Phosphate binders such as calcium carbonate or calcium acetate are most commonly used. Aluminum hydroxide is another phosphate binder but carries the risk of aluminum accumulation and toxicity in renal-failure patients whose renal aluminum excretion is impaired. In patients with concomitant hypercalcemia, sevelamer, a polymeric phosphate binder, can be used to treat hyperphosphatemia without further exacerbating the hypercalcemia.[12]

Magnesium Homeostasis

About 67% of magnesium is in the bones, 31% is intracellular, and only 2% is in the extracellular fluid. Most intracellular magnesium is bound to proteins and phosphate compounds. About 60% of

magnesium in the plasma is in its free form, 25% is protein-bound, and 15% is complexed to anions. The kidneys, bones, and gastrointestinal tract regulate magnesium homeostasis. Magnesium is primarily excreted by the kidneys. Magnesium is freely filtered in the glomerulus, with about 20%–30% reabsorbed in the proximal tubule, and up to 50% is reabsorbed in the thick ascending loop of Henle.[18] Only about 2% of magnesium is eliminated in stools.[19]

Magnesium Imbalances

In oliguric and anuric ARF patients, reduced renal magnesium elimination may result in hypermagnesemia. Clinical manifestations of hypermagnesemia depend on serum magnesium levels. Symptoms may affect the neuromuscular (lethargy, nausea, confusion, muscle weakness), cardiovascular (hypotension, arrhythmias, cardiac arrest), respiratory (respiratory depression), and neurologic systems. Primary treatment of hypermagnesemia is the removal of magnesium sources. In addition, administering loop diuretics increases renal magnesium elimination. Symptomatic patients should be treated with IV calcium chloride or calcium gluconate injection to antagonize and reverse the cardiovascular and neuromuscular effects of magnesium.[15]

Calcium Homeostasis

Calcium has many functions, including its role in bone metabolism, blood coagulation, platelet adhesion, neuromuscular activity, endocrine and exocrine secretory functions, and electrophysiology of heart and smooth muscles. Most of body calcium is in the bones. Because approximately 45% of serum calcium is bound to albumin, total serum calcium levels should be adjusted for serum levels. For each 1 g/dL of serum albumin below 4 g/dL, total serum calcium decreases by approximately 0.8 mg/dL. Corrected serum calcium levels can be estimated as follows:

Corrected serum calcium = measured serum calcium + 0.8 × (4 − measured albumin).

Because this equation may not accurately correct for total serum calcium levels especially with very low serum albumin levels, measurement of serum ionized calcium is recommended. Serum ionized calcium levels should be also interpreted in light of the acid-base status. Metabolic alkalosis increases calcium binding to serum proteins and lowers the serum ionized calcium levels. Metabolic acidosis has the reverse effect and decreases calcium binding to serum proteins, resulting in increased serum ionized calcium levels.[20,21]

Calcium Imbalances

In general, calcium disorders are not a major problem in ARF as with chronic renal failure (CRF).

Hypocalcemia may occur more commonly than hypercalcemia in ARF patients. The presence of hypercalcemia in ARF patients should prompt ruling out other causes such as malignancy, primary hyperparathyroidism, adrenal insufficiency, vitamin D toxicity, or milk-alkali syndrome. Hypercalcemia may also be caused by prolonged immobility. Hypercalcemia as a cause of ARF should also be ruled out.

Cases of hypocalcemia in ARF patients are mainly because of hypoalbuminemia and do not need treatment. Other causes of hypocalcemia may include hypoparathyroidism, hypomagnesemia, acute pancreatitis, malabsorption, hyperphosphatemia, loop diuretics, liver disease, vitamin D deficiency, and citrated blood transfusions.[12] Clinical manifestations of hypocalcemia are variable and depend on the acuity of the decrease in serum ionized calcium levels. The hallmark sign of hypocalcemia is tetany. Symptoms may affect the neuromuscular (cramps, perioral paresthesias, weakness), central nervous system (confusion, fatigue, seizures, hallucinations) and cardiovascular (hypotension, QT prolongation) systems. Acute or severe hypocalcemia requires treatment with IV calcium gluconate or calcium chloride. Calcium gluconate is less irritating to the veins than calcium chloride and is the IV calcium of choice for peripheral vein administration. Calcium chloride should be administered *via* a central venous access because severe phlebitis and tissue necrosis may occur if administered *via* a peripheral vein.[12]

Acid-Base Disorders

The kidneys play a significant role in the regulation of acid-base balance. This is because of the buffering systems found along the kidney tubules such as the Na^+-H^+ pumps, ammonia and ammonium systems, phosphates, bicarbonates, and organic acids that regulate acid-base homeostasis. In oliguric and anuric ARF, metabolic acidosis develops quickly. Metabolic acidosis results from the inability of the kidneys to excrete hydrogen ions at the distal tubule, inadequate bicarbonate synthesis and reabsorption at the proximal tubule, decreased ammonia production by the kidneys, and depletion of available buffers. Failure of acid excretion results in increased anion gap. The normal daily acid production of about 1 mEq/kg causes reduction by 1 mEq/L of serum bicarbonate, resulting in bicarbonate deficit. A catabolic state that is typical of ARF may further worsen the metabolic acidosis, which in turn hastens protein catabolism and muscle wasting. Dialysis and administration of bicarbonate in these patients would correct the metabolic acidosis. The reversal of metabolic acidosis has been shown to halt acidosis-related muscle wasting and improve nutritional status.[22–26]

Dialytic Intervention for ARF

A proactive and aggressive approach to the initiation of dialytic intervention is recommended to mitigate the metabolic derangements of ARF.[7,27] There is controversy regarding the indications for intermittent hemodialysis (IHD) *vs* CRRT in the management of ARF.[7] The advantages of CRRT compared with IHD include superior uremic and metabolic control; improved hemodynamic stability and gas exchange; better fluid control; and facilitation of sufficient nutrition support without the need for protein, fluid, and electrolyte restrictions.[3,7] Disadvantages of CRRT include the need for continuous anticoagulation and patient immobility.[7] Although the immediate costs of CRRT may be as high as 2.5 times the cost of IHD, long-term costs of CRRT are actually less expensive than IHD and can lead to improved renal recovery.[3]

CRRT

Indications for CRRT

Although an individualized approach is ideal, an established set of indications for the initiation of CRRT exists. Indications for CRRT include nonobstructive oliguria or anuria, severe metabolic acidosis, azotemia, severe hyperkalemia, suspected uremic organ involvement (pericarditis, encephalopathy, neuropathy, myopathy), severe dysnatremia, uncontrolled hyperthermia, diuretic-resistant edema or anasarca, drug overdose with a dialyzable toxin, and coagulopathy requiring large amounts of blood components in patients with or at risk of pulmonary edema or acute respiratory distress syndrome.[6,9,28–30]

Technology and Principles of CRRT

The technology of CRRT has undergone remarkable growth over the last 25 years. In many ICUs, especially in Australia and Europe, CRRT is the primary, if not exclusive, form of dialytic intervention used for ARF.[27] Once proper vascular access has been established using a dual-lumen central venous catheter specifically designed for dialysis, blood flows through a semipermeable membrane called a hemodiafilter. Blood flow is pressure driven either by using a peristaltic pump during venovenous hemodiafiltration or by relying on the patient's own blood pressure during arteriovenous hemodiafiltration. The hemodiafilter consists of a high- or low-flux synthetic membrane. When blood passes through the hemodiafilter, removal of fluid and solutes can be achieved by diffusion, convection, or a combination of both, depending on the CRRT modality used.[1,29]

CRRT encompasses dialytic modalities that differ according to the mechanisms used to achieve fluid and solute clearance. Significant practice variations exist with respect to CRRT.[3] In the interest of standardization and clarity, it is recommended to use the proposed nomenclature and common terms related to CRRT as defined by a consensus panel of experts (Table 1).[31]

The 4 most commonly used CRRT modalities are continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodiafiltration (CVVHDF), and slow continuous ultrafiltration (SCUF) (Table 2). Continuous arteriovenous therapies were originally used because they did not need a peristaltic pump, but the morbidity associated with arterial cannulation has led to their wide abandonment.

During CVVHD, solutes are removed primarily by diffusion across a semipermeable membrane. Diffusion is concentration gradient dependent. CVVHD uses the same principle as IHD with a dialysate that runs countercurrent to the blood on the other side of the hemodiafilter. CVVHD is used in situations where the main goal is to control blood concentrations of small solutes like urea, creatinine,

Table 1
Important nomenclature and common terms related to continuous renal replacement therapy[31]

Term	Definition
Diffusion	Solute and plasma water removal generated by a concentration gradient
Convection	Solute and plasma water removal generated by a pressure gradient
Ultrafiltration	A process whereby plasma water and solutes are separated from the blood across a semipermeable membrane that is driven by transmembrane pressure
Ultrafiltrate	The plasma water and solutes produced by ultrafiltration of the blood during continuous venovenous hemofiltration
Effluent	The plasma water and solutes produced by dialysate during continuous venovenous hemodialysis or continuous venovenous hemodiafiltration
Dialysate	A solution that passes through the hemodiafilter to achieve plasma water and solute clearance by diffusion
Venovenous circuit	Venous vascular access and associated tubing designed to carry blood into the hemodiafilter and back into circulation
Predilution (prefilter)	The administration of fluid into the patient's blood before it enters the hemodiafilter
Postdilution (postfilter)	The administration of fluid into the patient's blood after it leaves the hemodiafilter

Table 2
Advantages and disadvantages of various continuous renal replacement therapy (CRRT) modalities

CRRT modality	Advantages	Disadvantages
Continuous venovenous hemodialysis -Diffusion	Efficient removal of small molecular weight solutes (urea)	Moderate efficiency
	Replacement fluids are unnecessary	Dextrose-containing dialysate can be a significant caloric source
Continuous venovenous hemofiltration -Convection	Moderate efficiency in removal of middle-molecular-weight solutes	Significant (10%–17%) protein losses in ultrafiltrate
	Excellent fluid removal	Replacement fluids are necessary
Continuous venovenous hemodiafiltration -Convection and diffusion	Greatest efficiency in removal of middle molecular weight solutes and fluid	Significant (10%–17%) protein losses in ultrafiltrate
	Adjuvant therapy in the management of severe sepsis	Replacement fluids are necessary
		Dialysate can be a significant caloric source
Slow continuous ultrafiltraton -Convection	Safe and effective management of fluid overload	Low efficiency of solute removal

or electrolytes. Diffusion depends on the concentration gradient, molecular weight (speed, size), membrane resistance (material: high-flux membranes, thickness, number and size of pores), and protein-bound membrane toxins (solute-free fraction).[29]

With CVVH, dissolved solutes not restricted by the pore size of the membrane are transported along with the solvent *via* a solvent drag mechanism called convection. This filtration is directly proportional to the ultrafiltration rate at which plasma water traverses the semipermeable membrane and to the permeability of the membrane. Ultrafiltrate is the plasma water and ultrafiltered solute produced during hemofiltration. If the size of the dissolved solute is less than the diameter of the hemodiafilter pores (<15,000 daltons) the solute is removed by convection. Consequently, hemofiltration is more effective than IHD in removing higher-molecular-weight substances. A pressure gradient pushes blood through the hemodiafilter to remove plasma water (ultrafiltrate). The ultrafiltrate must be replaced with a solution that contains adequate amounts of fluid and electrolytes.[29]

CVVHDF combines diffusion and convection using a highly efficient hemodiafilter to remove both solute and fluid.[8] Both dialysate and replacement fluids are required with this modality. The convective process of solute and fluid removal accomplished with both CVVHDF and CVVH is referred to as ultrafiltration. Convective solute removal during CVVHDF and CVVH is influenced by solute size and membrane permeability. This aspect of solute removal is defined as the sieving coefficient, which is the degree to which a particular solute passes through the hemofilter membrane.[8] Sieving coefficients can range from 0 to 1.[8] A solute with a sieving coefficient of 1 will fully penetrate the membrane, whereas a solute with a sieving coefficient of 0 will be rejected from the membrane.[8] Unfortunately, the hemodiafilter cannot discriminate between uremic toxins and nutrients; therefore, the loss of nutrients with both CVVHDF and CVVH can be significant.[8]

Not only do CVVHDF and CVVH offer optimal removal of uremic toxins and fluid, they provide clearance of middle-molecular-weight molecules such as mediators of the inflammatory response, which is why CRRT may have a role in the therapeutic management of sepsis.[3,7,29]

SCUF is a version of CVVH that uses convection to provide management of fluid overload in patients with or without ARF.[29,31] SCUF primarily addresses fluid removal and offers minimal solute removal. For this reason, neither dialysate nor replacement fluids are components of this modality.[29,31] In facilities where CRRT is not readily used, sustained low-efficiency dialysis has emerged as a hybrid technique where IHD is run for 6–12 hours per day to achieve solute and fluid removal.[7,29] This approach uses standard IHD principles and equipment performed over an extended period in patients who are not hemodynamically stable enough to tolerate the physiologic demands of a traditional 3- to 4-hour run.

In general, solute clearance is weakest in techniques that use convection alone (CVVH, SCUF).[32] Diffusive techniques, such as CVVHD, offer enhanced solute clearance. The combination of convection and diffusion, as with CVVHDF, provides the greatest clearance of both fluid and solutes.[32] In the absence of conclusive head-to-head trials comparing one CRRT modality to another, the selection of specific CRRT modalities is often based on the availability of resources and physician preference.[6,7,29]

Four technical aspects of CRRT that that deserve special consideration because of their relevance to nutrition are dialysate solutions, anticoagulation, replacement fluids, and hypothermia.

Dialysate Solutions Used During CRRT

Several different dialysate solutions are commercially available for use with CRRT (Table 3). Many institutions design customized dialysate solutions

Table 3
Commercial dialysate solutions available for use with continuous renal replacement therapy

Dialysate	Normocarb	Premixed Dialysate for CVVHDF	1.5% Dianeal, low calcium	PrismaSate BGK2/0	PrismaSate BGK0/3.5	PrismaSate BGK4/0	PrismaSate BGK 4/2.5	PrismaSate LGK 0/2.5
Manufacturer	Dialysis Solutions Inc, Ontario, Canada	Baxter Healthcare Corp, Deerfield, IL	Baxter Healthcare Corp	Gambro Renal Products, Inc, Daytona Beach, FL	Gambro Renal Products, Inc	Gambro Renal Products, Inc	Gambro Renal Products, Inc	Gambro Renal Products, Inc
Sodium (mEq/L)	140	140	132	140	140	140	140	140
Potassium (mEq/L)	0	2	0	2	0	4	4	0
Chloride (mEq/L)	106.5	117	95	108	109.5	110.5	113	109
Bicarbonate (mEq/L)	35	0	0	32	32	32	32	0
Lactate (mEq/L)	0	30	40	3	3	3	3	35
Dextrose (mg/dL)	0	100 (0.1%)	1500 (1.5%)	110 (0.11%)	0	110 (0.11%)	110 (0.11%)	110 (0.11%)
Phosphate (mEq/L)	0	0	0	0	0	0	0	0
Magnesium (mEq/L)	1.5	1.5	0.5	1	1	1.5	1.5	1.5
Calcium (mEq/L)	0	3.5	2.5	0	3.5	0	2.5	2.5

CVVHDF, continuous venovenous hemodiafiltration; BGK, bicarbonate glucose potassium; LGK, lactate glucose potassium.

that are tailored to various CRRT modalities, equipment, and anticoagulation systems. Dextrose-containing dialysate solutions have been used with CVVHD and CVVHDF, containing a final dextrose concentration ranging from 1.5% to 2.5%, which can represent a significant caloric source.[1,8,32,33] The amount of glucose transferred across the dialysis membrane can range from 35% to 45% or higher, depending on the final dextrose concentration and several interacting variables such as the dialysate flow rate, the blood filtration rate, the ultrafiltration rate, and the patient's blood glucose concentration.[8,32,33] For example, 1 L per hour of dialysate containing a final concentration of 1.5% dextrose at 43% uptake yields the net absorption of approximately 526 kcal/d.[1,32] Likewise, 1 L per hour of dialysate containing a final concentration of 2.5% dextrose at 45% uptake yields the net absorption of approximately 918 kcal/d.[1,32] To promote glycemic control and avoid overfeeding, nutrition-support regimens must be modified accordingly to account for obligatory caloric delivery when dextrose-containing dialysate solutions are used.[8,32,33] A better strategy is to use low-dextrose dialysate solutions containing a physiologic concentration of dextrose (0.1% to 0.15%).[8,32,33] These dialysate solutions do not provide significant dextrose calories; in fact, they can result in a 4% net loss of glucose from the patient.[34]

Anticoagulation

Multiple strategies are devised to prevent clotting within the extracorporeal circuit and maintain the patency of the hemodiafilter to avoid frequent interruptions of CRRT. Several forms of anticoagulation are used during CRRT to extend the life of the hemodiafilter. These include unfractionated heparin, 4% and 2% trisodium citrate, and anticoagulant citrate dextrose-formula A (ACD-A). Heparin is the most commonly used anticoagulant but has the disadvantages of causing systemic anticoagulation, which increases the risk of bleeding and is contraindicated in patients with heparin-induced thrombocytopenia.[35–38] Heparin may also be contraindicated in patients with liver failure and coagulopathies who are at high risk for bleeding. To avoid these effects, trisodium citrate has become more commonly used as an alternative anticoagulant to heparin. Trisodium citrate is used for regional anticoagulation within the extracorporeal circuit and has also proven to extend the life of the filter longer than heparin.[37,39] Trisodium citrate, infused prefilter, exerts its anticoagulant effect through chelation of ionized calcium, which is a cofactor in the coagulation cascade.[40] Because the formed citrate-calcium complex is mostly eliminated in the ultrafiltrate, hypocalcemia is the major complication of trisodium citrate. As such, calcium chloride is continuously infused during the process, and the infusion is adjusted according to the serum

ionized calcium levels. The citrate portion that is not cleared in the ultrafiltrate is subsequently metabolized to bicarbonate in the liver. As such, the patient's acid-base status is closely monitored to avoid alkalemia. Because citrate conversion mainly occurs in the liver, patients with liver failure may accumulate citrate, possibly causing anion-gap metabolic acidosis and an increased total calcium/ionized calcium ratio of >2.5.[41–43] The possibility and severity of citrate toxicity in patients with liver failure remains, however, to be determined.[43] Another anticoagulant used for regional anticoagulation is ACD-A. ACD-A has also been shown to extend the life of the hemodiafilter and is associated with lesser metabolic complications than trisodium citrate.[40,44]

When evaluating the nutritional requirements of a CRRT patient, it is important to consider the composition of the anticoagulant and the potential implications of these solutions. In an effort to assist the reader to investigate some of these issues, a checklist to evaluate CRRT practices is included (Table 4).

Replacement Fluids Used During CRRT

CRRT modalities that need fluid replacement include CVVH and CVVHDF because of their dependency on convection for clearance. Replacement fluids given prefilter minimize procoagulation and hemoconcentration.[29] The selection of replacement fluids should be individualized to meet the metabolic demands of the patient. Factors that should be taken into consideration include the type of dialysate and anticoagulation being used for CRRT, the electrolyte status, and acid-base balance of the patient. Depending on the concentration of sodium, potassium, and magnesium in the dialysate solution (Table 3) and the serum electrolyte levels of the patient, management of these electrolytes may be achieved by adding adequate amounts to the replacement fluid. Examples of commonly used replacement fluids include normal saline, 0.45 normal saline, sodium bicarbonate, or dialysate solutions.

Table 4
Checklist to evaluate continuous renal replacement therapy (CRRT) practices used at your institution

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✓ Does the patient have indications for the initiation of CRRT?
✓ What CRRT modality is used?
✓ What is the composition of the dialysate, depending on the CRRT modality?
✓ What form of anticoagulation is used?
✓ What form of anticoagulation should be used in patients with liver failure undergoing CRRT?
✓ What is the composition of the replacement fluids according to the CRRT modality?
✓ How is hypothermia being addressed in patients undergoing CRRT?

Hypothermia

Hypothermia is a side effect of CRRT that occurs with an incidence of 2%–50% of patients and is defined as a core temperature $<35°C$.[45,46] The primary mechanism by which CRRT causes hypothermia is heat loss. Heat is lost to the atmosphere, through blood tubing, the surface of the hemofilter, the effluent flow, and through the interaction of the patient's blood with room-temperature dialysate and replacement fluids.[46]

Hypothermia can mask one of the first signs of infection by inhibiting the patient's ability to mount a fever. Other side effects of hypothermia include the compromise of host immune defenses; increases in systemic vascular resistance and mean arterial pressure; and decreases in heart rate, cardiac output, and systemic oxygen delivery.[46] Hypothermia has been linked with higher infection rates in critically ill patients.[45,47,48] Conversely, prevention of hypothermia in surgical patients has been found to decrease postoperative wound infections.[29] Warming blankets are often used to rewarm patients with hypothermia. However, the ideal practice would be to prevent hypothermia, rather than treat it, by using a fluid warmer as a companion to the CRRT machine.

Specialized Nutrition Support in Patients Treated With CRRT

Primary nutritional goals in the management of ARF are maintenance or improvement of nutritional status without exacerbating metabolic derangements, enhancement of wound healing, optimal resistance to infection, and reduced mortality.[1] The nutritional implications of CRRT are significant and vary with the type and intensity of each modality.[10]

Nutrition Assessment

The assessment and diagnosis of malnutrition is difficult in patients with ARF.[5] Body weight, body mass index, anthropometric measurements, and serum protein levels are of little value in the nutrition assessment of these critically ill, fluid-overloaded patients.[1] Subjective global assessment (SGA) is a simple tool with high sensitivity and specificity that is composed of a carefully organized outline of a patient's dietary and past medical history, physical examination, and functional assessment.[49,50] Using SGA in a prospective noninterventional study, Fiaccardori et al[5] found that 42% of patients with ARF requiring CRRT had severe malnutrition and that preexisting malnutrition was a statistically significant and independent predictor of a negative hospital outcome. Even though traditional nutrition assessment tools may be unreliable for this population and SGA is not widely used by ICU clinicians, it must be recognized that malnutrition is highly prevalent in patients with ARF.

Protein Requirements During CRRT

The delivery of adequate protein to patients with ARF is an important component of the nutritional regimen because of their hypercatabolism,[6] obligatory use of protein as a preferred fuel source during the stress response,[2] and the likelihood of significant protein losses in CRRT effluent.[1,2] The high-flux membrane used within the hemodiafilter is permeable to plasma proteins. Protein losses are higher during convection-based (CVVH and CVVHDF) than diffusion-based (CVVHD) CRRT because of the type of membrane used with each modality.[2,51,52] In general, centrally infused protein losses into CRRT effluent range from 10% to 17% and should be taken into consideration when determining protein requirements.[27,34,53,54]

Consensus in the literature for protein delivery in patients undergoing CRRT is 1.5–2 g protein/kg.[1,7,32,33,53] However, up to 2.5 g/kg of protein has been advocated to promote positive nitrogen balance.[27,34,53,54] Disadvantages of high-protein delivery may include the exacerbation of uremia, increased demand on hepatic and renal function, and increased costs.[7,10,53]

Energy Requirements During CRRT

Energy expenditure is not greatly affected by ARF, in and of itself. The underlying pathology leading to the patient's critical illness plays the biggest role in determining energy expenditure.[1,2,6,10,27,32] The use of indirect calorimetry allows nutrition support to be tailored to the individual patient's needs and is the gold standard for determining energy expenditure in critically ill patients.[1,32,54,55] It is recommended to feed at no higher than 130% of the patient's resting energy expenditure.[1,10,52,55] Indirect calorimetry also facilitates the recognition of hypometabolism associated with CRRT. Hypothermia has been shown to influence energy expenditure by inducing a hypometabolic response in the patient.[32] The decrease in core temperature is associated with a 20% reduction in oxygen consumption, corresponding to a 7.1% decrease in energy expenditure.[32,56] A potential limiting factor related to indirect calorimetry is that CRRT may result in extracorporeal removal of CO_2, but whether or not these losses are significant enough to affect the validity of indirect calorimetry is unclear.[54,55,57–59] In the absence of IC, many equations exist for predicting the caloric requirements of critically ill patients. Clinical consensus is to provide CRRT patients with 25–35 kcal/kg.[7,10,27]

The avoidance of overfeeding is crucial in these patients.[10] Nutrition-support regimens must be modulated around obligatory calories from CRRT dialysate, anticoagulation, replacement fluids, and other dextrose- or lipid-containing IV medications, when indicated. Low-dextrose dialysate solutions are available and should be used whenever possible to avoid overfeeding, promote glucose control, and minimize the need to modulate nutrition regimens.

Enteral Nutrition During CRRT

The initiation of nutrition support should begin as soon as feasible after resuscitation and hemodynamic stabilization. As with most ICU populations, the enteral route is the preferred route for nutrition support in patients with ARF because it can preserve gut function, possibly enhance immunity, and decrease episodes of bacteremia and infection.[2,6,10,27] Small bowel enteral access is beneficial because this population is likely to develop gastroparesis and may not always tolerate elevation of the head of bed >30 degrees. Low infusion rates using a standard polymeric formula are appropriate until tolerance is assured.[10,32,60] When diluted standard enteral formulas are used to account for obligatory calories from dextrose-containing dialysate, modular protein is often needed to meet protein goals without overfeeding from a caloric standpoint.[32,33] Enteral formulas designed for renal failure are unwarranted because fluid, protein, and electrolyte restrictions become unnecessary during CRRT.[60] The use of "wound-healing" enteral formulas is controversial because of their high vitamin A and vitamin C content. Additional water-soluble vitamins should be administered to replace CRRT losses by using a renal multivitamin delivered *via* the patient's nasogastric tube.[1,2,6]

It has been theorized that patients undergoing CRRT may benefit from immune-enhancing enteral formulas.[6,27] Most patients requiring CRRT are metabolically stressed, with altered immune function. Immunostimulatory nutrients like arginine and nucleotides may exacerbate the proinflammatory response counterproductively, especially in patients with sepsis.[61,62] Caution is warranted with the use of immune-enhancing nutrients in patients having undergone solid organ transplants because of their immunostimulatory functions, which could increase risk of organ rejection. In view of the lack of randomized controlled studies evaluating the effects of immune-enhancing nutrients in patients with ARF receiving CRRT, recommendations on this subject cannot be provided at this time.[10]

Monitoring tolerance to enteral nutrition is vital to the avoidance of nutrition-related complications. Clinical abdominal examinations should be followed for signs of ileus, abdomen distention, or pain. Caution should be used in patients receiving enteral feedings during acute hypotension or hemodynamic instability requiring vasopressor support.[63,64] Dual support with parenteral nutrition (PN) and tube feeding in order to achieve the benefits of enteral nutrition while meeting target calories and protein with PN is an acceptable approach, when indicated.[2,6,10,54] Indeed, the majority of the prospective, randomized, controlled trials evaluating nutrition during CRRT used PN as the route of nutrition support. Very few

systematic studies on enteral nutrition and the impact of ARF on gastrointestinal function have been published. However, in a prospective, multicenter cohort study, Metnitz et al[4] reported that enteral nutrition was associated with improved survival in patients undergoing CVVH and CVVHDF. A subsequent study corroborated their findings by further demonstrating that the presence of enteral feeding, even after adjusting for predicted risk of death, had a statistically significant benefit on outcome in CRRT patients.[54]

PN During CRRT

PN is appropriate when the gastrointestinal tract cannot be used for enteral feeding. A balanced PN regimen usually provides 10%–20% of total daily calories from amino acids, 50%–60% of calories from dextrose, and 20%–30% of calories from lipid emulsions. Designer amino acid formulations are expensive and offer no clinical benefit to patients receiving CRRT.[27] Limiting dextrose infusion rates to ≤4–5 mg/kg/min in adult patients is indicated in critically ill adult patients.[65,66] The modulation of amino acids and dextrose around obligatory loss and net absorption from CRRT is an important aspect of designing PN regimens. However, it should be noted that there are negligible lipid losses across the hemodiafilter.

Lipid clearance may be reduced in critically ill ARF patients because of decreased activity of the lipoprotein lipase enzyme.[10] Lipid administration should be limited to <1 g/kg/day, with the routine measurement of serum triglyceride levels to avoid hypertriglyceridemia.[2,3,10] The 20%–30% lipid emulsions have a lower potential for hypertriglyceridemia than the 10% emulsion because of their lower phospholipid content.[67,68] Withholding lipid infusion is recommended when serum triglyceride levels are >400 mg/dL in adult patients. Providing 300 mL of 20% lipid biweekly prevents essential fatty acid deficiency. In theory, the use of parenteral medium-chain triglycerides (MCT) may result in lower serum triglyceride levels than long-chain triglycerides (LCT) because of their faster oxidation. However, the benefits of using mixed MCT/LCT lipid formulation in ARF patients are yet to be determined.[69] At this time, MCT/LCT lipid formulations are not commercially available in the US.

Typically, restriction of potassium, magnesium, and phosphorus in PN is unnecessary for CRRT patients. Serum electrolyte levels are largely dictated by the electrolyte composition of the dialysate solutions and the efficiency of CRRT in solute clearance. Losses of potassium, calcium, phosphorus, and magnesium in CRRT effluent and urine should be anticipated and treated aggressively. The development of profound hypophosphatemia during uninterrupted CRRT, especially with use of CVVHDF, because of hyperexcretion and intracellular shifting is predictable and should be treated accordingly.[32] The chloride:acetate ratio can be adjusted in PN according to acid-base status. Maximizing acetate, a bicarbonate precursor, in PN helps correct the metabolic acidosis, but this should be weighed against other acetate, citrate, or bicarbonate sources related to CRRT.

Supplementation of vitamins and trace elements in ARF is largely derived from data in patients with CRF. Vitamins[70] and trace elements[71] are usually added to PN according to the recommendations of Nutritional Advisory Group to the American Medical Association. Commercially available parenteral vitamin products contain a mix of water- and fat-soluble vitamins and are generally adequate for most ARF patients.

Trace Elements in ARF Patients

Trace-element requirements for ARF patients treated with CRRT represent an important area of research. Most recommendations regarding mineral requirements during ARF are extrapolated from research conducted in CRF patients. Of the available studies, many of the findings on trace-element homeostasis in ARF represent unspecific alterations within the spectrum of acute-phase response, and these alterations may not necessarily reflect specific effects induced by ARF.

Alterations in blood and tissue trace element levels have been described in CRF patients undergoing IHD.[72–78] Increased[72,74] or decreased plasma zinc levels,[75,76,78] increased plasma copper levels,[72,74,76,78] and decreased plasma and erythrocyte selenium levels[72,77] have been reported. A possible zinc deficiency–induced gonadal dysfunction in IHD patients has been proposed, which was reversed by adequate zinc supplementation.[79] Zinc supplementation caused reversal of hypogeusia observed in CRF patients.[80] Zinc supplementation may also improve lymphocyte function because of zinc deficiency in uremic patients by possibly correcting this abnormality.[81] However, the potential for these alterations, their clinical implications, and the response to zinc supplementation are largely unknown in patients with ARF.

Reduced serum selenium levels in CRF patients were associated with a lower platelet glutathione peroxidase activity and possible increase in cardiovascular complications compared with the patients without cardiovascular complications.[82] Because data on trace element abnormalities are mostly derived from CRF patients, it is difficult to extrapolate these data to ARF patients who may have other concurrent diseases and are on a shorter duration of dialysis.[83] Also, historically, there have been difficulties in assessing trace element status in ARF patients. This is because of several factors, including trace-element tissue redistribution during stress, changes in trace element plasma protein binding, methodological assay difficulties, and questionable correlation between blood trace-element levels and tissue stores.

Trace Elements in CRRT Patients

Trace elements have small molecular weights to pass through the hemodiafilter membranes, and alteration in plasma protein binding during critical illness could affect trace-element homeostasis during CRRT therapy. *In vitro* data showed that trace elements, including selenium, chromium, copper, and zinc, are cleared during CVVH. Manganese removal by CVVH appears to be least affected, whereas significant selenium clearance occurs.[84]

Few studies evaluated the behavior of trace elements in CRRT patients.[85–88] Van Renterghem et al[85] evaluated the effects of CVVHDF on the serum levels of 12 minerals in 5 patients. Lower serum selenium and zinc levels and higher serum copper levels compared with reference values were reported. Dialysate concentrations of copper and zinc were lower than the corresponding serum values, and selenium levels were below the detection level of the analytical methods. The replacement fluid contained very low concentrations of copper, selenium, and zinc, below those for respective serum levels. The investigators concluded that the low serum selenium and zinc levels were caused by their low concentrations in the replacement fluid. It was also suggested that the high serum copper levels were not related to CVVHDF because of low and constant dialysate and replacement fluid values but were rather related to copper and zinc competition to plasma protein binding. Limitations to this study include a small sample size, the absence of baseline serum mineral levels before initiation of CVVHDF, and failure to measure trace mineral levels in the spent dialysate.

In a larger study by Story et al,[86] blood trace element levels were measured in 9 normal subjects, 9 ICU patients, and 8 ICU patients treated with CVVH. In the CVVH group, blood samples were collected before CVVH initiation and at 30 minutes and 24 hours after CVVH initiation. Ultrafiltrate samples were collected at 30 minutes and 24 hours after CVVH initiation. Study results showed a statistically significant reduction in blood selenium and zinc levels in the CVVH group compared with controls. Chromium and copper losses occurred in the ultrafiltrate. However, chromium blood levels were increased. Ultrafiltrate losses of manganese, selenium, and zinc were small or undetectable, and the investigators concluded that the significance of ultrafiltrate loss of these trace elements was unclear. There was no report on whether selenium, manganese, and zinc were present or not in the ultrafiltrate, and it was unknown whether patients were receiving nutrition as a potential source of trace elements.

In a study of trauma patients treated with CRRT, zinc losses occurred with CVVH and CVVHD.[87] Study results showed a small amount of zinc in the effluent with both CVVH and CVVHD. Trisodium citrate was used as an anticoagulant, which was contaminated with 6.2 ± 0.4 μmol/L of zinc. This contamination could have influenced the study results. Because minimal amounts of zinc were detected in the ultrafiltrate, the investigators concluded that zinc losses did not amount to providing additional zinc to patients treated with CRRT who are receiving standard zinc amounts in their PN.

In a prospective, randomized, crossover study, Berger et al[88] evaluated the effects of CVVHDF on the elimination of copper, selenium, and zinc in 11 critically ill adult patients with ARF. Each patient received 2 different replacement fluids, including bicarbonate and lactate solution. Patients were receiving PN with micronutrient supplements. Plasma trace element levels were collected at baseline and at the end of the CRRT session. The effluent solution was also analyzed for trace element levels. Study results showed that all 3 elements were eliminated in the effluent. Most significant was the elimination of selenium at 2 times the daily supplemented intake. Because selenium is a cofactor for the antioxidant glutathione peroxidase enzymes, it is of concern that selenium deficiency may result in decreased antioxidant defense activities. About 30% of the supplemented copper in PN was lost. Although zinc was lost in the effluent, a positive zinc balance was reported. The investigators related the positive zinc balance to zinc contaminants in replacement fluids, which provided zinc in addition to what was normally added to PN. Only very small quantities of selenium and no measurable amounts of copper were detected in the replacement fluids.

In summary, plasma levels of trace elements seem to be altered during CRRT. The ultrafiltration rate appears to be a significant factor affecting trace element clearance during CVVH.[84] According to the few available studies, the extent of trace element clearance has been variable. This variation may be affected by the type of CRRT used, patient population, duration of CRRT, and the sensitivity of assay methods used for measuring trace elements. Further studies are needed to assess the clinical impact of changes in trace-element levels and to determine the actual requirements of trace-element supplementation during CRRT.

Vitamins in CRRT Patients

CRRT primarily affects water-soluble vitamins, but fat-soluble vitamins are unlikely to be affected.[10,27] Loss of water-soluble vitamins during dialysis has been reported. Berger et al[88] reported significant losses of thiamin in the effluent during CVVHDF therapy in critically ill ARF patients. The elimination of thiamin exceeded 1.5 times the standard daily provision of thiamin in the parenteral multivitamin mix. Vitamin C losses may also occur during CRRT at a level that is equivalent to the RDI.[27] In the study by Story et al,[86] vitamin C was detected in the ultrafiltrate during CVVH therapy. Decreased blood levels of vitamin C and vitamin E were also

reported.[86] However, the clinical significance of these changes is unknown. Vitamin C administration should be given cautiously because of risk of oxalate crystallization.[27] The current recommendation is to limit vitamin C intake to ≤200 mg/day.[10] Commercial parenteral multivitamin formulations have been reformulated to contain 200 mg vitamin C. Vitamin C has many physiologic functions, including its role as an antioxidant. Whether additional vitamin C is required during CRRT remains to be determined. Additionally, there may be depletion of other endogenous antioxidants in ARF.[27] However, the role of antioxidant supplementation in ARF patients undergoing CRRT is unknown.[10,89]

There is a theoretical concern about vitamin A accumulation and potential toxicity in renal-failure patients. Elevated serum vitamin A and retinol-binding protein levels occur in patients receiving dialysis because of reduced renal metabolism of these substances in renal failure. This mainly may become a problem in CRF patients. However, vitamin A toxicity, which is a factor of the free unbound serum vitamin A, is unlikely to occur during the relatively short time period of CRRT therapy.

In summary, more research is needed to determine the actual vitamin requirements in CRRT patients. Although losses of thiamin and vitamin C have been reported, the clinical impact of these losses remains unknown. Also, the behavior of other water- and fat-soluble vitamins is undetermined in this population.

Monitoring Parameters During Nutrition Support in Patients With ARF

Tight Glycemic Control

Hyperglycemia is common in critically ill patients with ARF as a consequence of insulin resistance and hepatic gluconeogenesis.[6,10] Poor glucose control may result in significant complications and increased infectious risk. In a landmark study by van den Berghe et al,[90] tight glycemic control was shown to decrease mortality in critically ill patients. The investigators also concluded that intensive insulin therapy prevented ARF.[90] However, the goal of maintaining glucose levels between 80 and 110 mg/dL is particularly challenging for ARF patients requiring CRRT. Patients receiving high dextrose loads from CRRT dialysate will absorb more dextrose when blood glucose levels are lower than the dialysate glucose concentration.[34] Conversely, when low dextrose dialysate solutions are used, glucose losses into the effluent will be directly proportional to blood glucose levels; therefore, losses can be decreased by tight glycemic control.[34] Significant amounts of insulin may be required by this population. The addition of regular insulin to PN may lead to hypoglycemia should CRRT become unexpectedly interrupted, especially if the dialysate or replacement fluids contain dextrose. Therefore, the safest approach to glucose control in CRRT patients is through a continuous regular insulin infusion, which allows hourly titration of insulin delivery according to the patient's clinical and metabolic status.

Acute Protein Status

Plasma protein levels may not be very useful as nutritional markers during the early phases of critical illness and ARF for several reasons. Hydration status will affect plasma proteins, which can manifest as either hemodilution or hemoconcentration of values.[2] The acute-phase response to metabolic stress that is so common in ARF patients is associated with the reprioritization of plasma protein synthesis within the liver, resulting in lower serum prealbumin and albumin levels, regardless of nutritional status. To corroborate whether various plasma proteins are low because of malnutrition *vs* the acute-phase response to inflammation, the measurement of C-reactive protein can be obtained as this plasma protein is a positive acute-phase reactant.[91] Following trends in plasma protein levels can be meaningful in this regard. However, because prealbumin is degraded in the healthy kidney, levels may be slightly higher in patients with ARF. As such, aiming for a prealbumin level >30 mg/dL would be the goal in achieving optimal plasma protein status for this population.[92]

Nitrogen-Balance Studies

Nitrogen-balance studies are widely used as the gold standard for assessing protein status and degree of catabolism *vs* anabolism among researchers, and yet the utility and accuracy of nitrogen-balance studies outside the research setting, for this population, is controversial. The reliability of urinary urea nitrogen (UUN) levels to accurately calculate nitrogen balance is compromised with creatinine clearance of <50 mL/min.[32] Interruptions in CRRT decrease the accuracy of 24-hour UUN measurements. UUN losses in effluent, dialysate, and any urine production must be accounted for in order for studies to be accurate.[32] An important question to ask is whether monitoring nitrogen balance would change what is given to the patient in terms of protein provision. Increasing protein delivery may reduce, but will not eliminate, cumulative nitrogen deficits.[32]

Patient Case

A 35-year-old white man presented to the emergency department with progressive shortness of breath after a recent "viral" illness. His past medical and surgical history were noncontributory. The patient was diagnosed with severe bacterial endocarditis affecting his aortic valve.

Nutrition Parameters

Nutrition parameters were as follows:
Height: 5 feet 11 inches
Actual body weight: 99 kg
Usual body weight: 89 kg
Ideal body weight: 78.2 kg
Predicted energy requirements: 2225–3115 kcal/day (25–35 kcal/kg)
Protein requirements for CRRT: 133–178 g/day (1.5–2 g/kg)

Hospital Course

The patient was emergently taken to the operating room for an aortic valve replacement. Postoperatively, he became hypotensive and hemodynamically unstable, requiring multiple vasopressors to support his blood pressure. His urine output fell to <400 mL per day, and did not respond to IV fluids, plasma expanders, or diuretic therapy. It became evident that the patient had developed prerenal ARF secondary to perioperative ischemia and renal hypoperfusion. On hospital day 2, CVVHDF was initiated using a 2.5% dextrose-containing dialysate (918 kcal/day net absorption), trisodium citrate for regional anticoagulation, and normal saline as replacement fluids. The patient developed hyperglycemia with the induction of CRRT, despite having no history of diabetes mellitus, and required an insulin drip to achieve tight glycemic control. By hospital day 8, the patient had become hemodynamically stable, and he began to make urine. As the patient became more alert and oriented, he self-extubated from mechanical ventilation, and he was successfully converted over to IHD for ongoing dialytic support 3 times per week. See Table 5 for laboratory and nutrition-related trends.

Nutrition Course

On hospital day 2, a nasoenteric feeding tube was placed into his small bowel to begin enteral nutrition support using a standard, isotonic formula. Enteral nutrition was not well tolerated by the patient secondary to hemodynamic instability, abdominal distention, and high nasogastric output.

Therefore, on hospital day 4, the tube feeding was decreased to 20 mL/h for gut stimulation, and PN was started with a solution containing 75 g protein, 50 g dextrose, and 10 g fat, which was modulated around obligatory calories from dextrose-containing dialysate and lipid-containing sedation (propofol). The PN electrolytes were geared toward his laboratory values (Table 5). Insulin was not added to the PN solution to protect the patient from hypoglycemia if the CRRT system was interrupted for any unforeseen reason. A renal multivitamin preparation was delivered *via* nasogastric tube to replace water-soluble vitamin losses *via* spent CRRT ultrafiltrate. On hospital day 5, PN was advanced to "goal" of 150 g protein (1.7 g/kg) and 2388 kcal/day, including dextrose calories absorbed from CRRT dialysate, according to indirect calorimetry, which revealed a resting energy expenditure of 2350 kcal/day. On hospital day 8, total PN was reformulated after the patient was converted to IHD to provide 125 g protein (1.4 g/kg) and 2345 kcal/day. Unfortunately, the patient inadvertently pulled out his central IV line for PN and nasogastric tube on hospital day 9 during a moment of agitation. After a successful bedside swallowing study on hospital day 10, the patient began receiving a renal diet, and a calorie count was ordered to document the adequacy of his oral intake. Pertinent medications included a renal multivitamin, phosphorus binder with meals, and a stool softener.

Conclusions

Nutrition support in critically ill patients with ARF is complex, and the metabolic alterations caused by the stress response, and the supportive therapies designed to treat it, must be taken into consideration in order to design optimal nutrition regimens for this population. The trend toward the use of CRRT as the dialytic modality of choice in the ICU for patients with ARF makes this area of nutrition practice of great interest to the clinician. By obtaining a solid foundation of knowledge about the nutritional implications of CRRT, the precision of nutrition support practices will undoubtedly improve the quality of care and clinical outcomes. A

Table 5
Patient case: nutrition parameters and indices

Hospital day	BUN mg/dL	Cr mg/dL	K+ mEq/L	Phos mg/dL	Mg++ mEq/L	I. Ca++ mg/dL	Caloric delivery	Protein delivery, g/d
2	37	3.6	6.3	6.5	1.6	3.7	918	0
3	40	4	4.5	5.6	1.4	2.9	2032	19
4	31	3.8	3.6	2	2	6	2602	94
5	33	3.9	4.1	3.7	1.9	5.1	2388	150
8	74	5.6	4.3	4.5	2.1	4.8	2345	125
10	89	9.5	3.9	8.3	2.2	3.6	2180	95

BUN, blood urea nitrogen; Cr, creatinine; K+, potassium; Phos, phosphorus; Mg++, magnesium; I. Ca++, ionized calcium.

Table 6
Summary of nutrition support recommendations for adult continuous renal replacement therapy (CRRT) patients

- Protein, fluid, and electrolyte restrictions are not necessary during CRRT.
- Protein requirements during CRRT have ranged between 1.5 and 2.5 g/kg reference weight.
- Indirect calorimetry is recommended to identify caloric needs of CRRT patients. Caloric delivery should provide 100%–130% resting energy expenditure.
- Otherwise, energy needs can be predicted using 25–35 calories/kg reference weight.
- Although the enteral route is preferred for nutrition support, parenteral nutrition (PN) may be indicated in the presence of gastrointestinal dysfunction or hemodynamic instability.
- Water-soluble vitamin supplementation is necessary for patients treated with CRRT.
- Standard multivitamin and trace element levels are appropriate with PN.
- Uninterrupted CRRT leads to a dramatic decline in serum magnesium, potassium, and phosphorus levels secondary to intracellular shifting and increased losses with ultrafiltration. Anticipation of these abnormalities can yield appropriate supplementation and electrolyte repletion.
- The safest approach to treat severe hyperglycemia in CRRT patients is through the use of a continuous regular insulin infusion.
- The nutrition regimen should be based on the changes that occur in the patient's clinical and metabolic status.

summary of our recommendations for nutrition support during CRRT can be found in Table 6.

Clinical research related to the nutrition implications of CRRT is still lacking, and many questions remain unanswered. The efficacy of enteral *vs* PN during CRRT needs further study. The use of indirect calorimetry and, hence, avoidance of under- or overfeeding on outcome is unknown in this population. The vitamin and trace element needs of ARF patients requiring CRRT are poorly understood. The role of immunonutrition and antioxidant therapy requires further elucidation.

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