Nutritional Management of Acute Renal Failure

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Acute renal failure (ARF) is associated with fundamental alterations of metabolism and immunocompetence with the induction of a pro-oxidative and proinflammatory state. Thus, the objectives of nutritional therapy include not only conventional goals such as maintaining lean body mass and stimulating immunocompetence and repair functions, but also mitigating the inflammatory state and improving the oxygen radical scavenging system and endothelial functions. Moreover, pre-existing and/or hospital-acquired malnutrition has been identified as an important factor contributing to the persistent high mortality in acutely ill patients with ARF. A nutritional program for a patient with ARF must consider not only the specific metabolic consequences associated with renal failure and with the underlying disease process, but also the profound alterations in nutrient balances induced by replacement therapy. Nutrient requirements thus may differ widely between individual patients and during the course of disease, and nutrition therapy must be coordinated with renal replacement therapy. Whenever possible, enteral nutrition should be provided in patients with ARF because even small amounts of luminal nutrients will help to maintain intestinal function. Nevertheless, in many patients parenteral nutrition, at least supplementary and/or temporarily, will become necessary. Because of the complex alterations in the use of various nutrients and the impaired tolerance to electrolytes and volume load, metabolic complications of nutritional support frequently occur in patients with ARF. Therefore, nutrition therapy must be more closely monitored in patients with ARF than with other diseases.

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A CUTE RENAL FAILURE (ARF) is a clinical syndrome with a high mortality rate. This impact of ARF on prognosis is closely related to the systemic immunologic and metabolic consequences of ARF, the induction of a pro-oxidative and proinflammatory state, which are aggravated by malnutrition. Thus, beyond conventional objectives such as the preservation of lean body mass and stimulation of immunocompetence, repair functions, and wound healing, nutritional interventions must be aimed at mitigating the inflammatory state, at improving the oxygen radical scavenging system and endothelial functions.

In designing a nutritional program for a patient with ARF, not only must the specific metabolic consequences associated with renal failure, the underlying disease process, and/or the associated complications be taken into consideration, but also the profound alterations in nutrient balances induced by modern replacement therapy. Nutritional support must be viewed as a crucial element in the complex therapeutic strategies in the care of the often–critically-ill patients with ARF, a metabolic intervention that must be coordinated with renal replacement therapy.

In the past, parenteral nutrition was the preferred route of nutritional support in patients with ARF. Recently, enteral nutrition has become the primary type of nutritional support for patients with ARF. Enteral nutrition may have specific advantages for patients with ARF. Moreover, even small amounts of luminaly provided diets can help to support intestinal functions. Nevertheless, in many patients it is not possible to meet requirements by the enteral route alone, and parenteral nutrition, at least supplemented and/or temporarily, may become necessary.

Metabolic Alterations and Nutritional Requirements in ARF

ARF not only affects water, electrolyte, and acid–base metabolism, but also induces a global
change of the “milieu interieur” with specific alterations in protein and amino acid, carbohydrate, and lipid metabolism, and in addition, exerts a proinflammatory reaction and a profound effect on the antioxidative system. Furthermore, ARF rarely is an isolated disease process, but most often is a complication of sepsis, trauma, or multiple-organ failure. Metabolic changes in these patients will be determined not only by ARF per se but also by the underlying disease process and/or complications and organ dysfunctions and, last but not least, by the type and intensity of renal replacement therapy.

The optimal intake of nutrients in patients with ARF thus is influenced more by the nature of the illness causing ARF, the extent of catabolism, and the type and frequency of renal replacement therapy than by ARF per se. It must be noted that patients with ARF are a heterogeneous group of subjects with widely differing nutrient requirements that can vary considerably during the course of disease.

**Energy Metabolism and Energy Requirements**

In patients with uncomplicated ARF, oxygen consumption is within the range of healthy subjects, and in the presence of sepsis or multiple-organ dysfunction syndrome may increase by approximately 25%. Thus energy expenditure in patients with ARF is determined by the underlying disease and not by renal failure.

Energy substrate supply should not exceed the actual energy requirements. Complications, if any, from slightly underfeeding are less deleterious than from overfeeding. Patients with ARF should receive 20 to 30 kcal/kg body weight/day. Even in hypermetabolic conditions such as sepsis or multiple organ failure, energy expenditure rarely is higher than 130% of calculated basic energy expenditure, and energy intake should not exceed 30 kcal/kg body weight/day.

**Carbohydrate Metabolism**

Frequently, ARF is associated with hyperglycemia. The major cause of elevated blood glucose concentrations is insulin resistance. Plasma insulin concentration is elevated; maximal insulin-stimulated glucose uptake by skeletal muscle is decreased. A second feature of glucose metabolism in ARF is accelerated hepatic gluconeogenesis, mainly from conversion of amino acids released during protein catabolism, that cannot be suppressed by exogenous glucose infusions.

Hyperglycemia in the critically ill has been recognized as an important determinant in the evolution of complications such as infections or organ failure and prognosis. Thus, maintaining normoglycemia must be strictly observed during nutritional support.

**Lipid Metabolism**

Profound alterations of lipid metabolism occur in patients with ARF. The triglyceride content of plasma lipoproteins, especially very-low-density lipoproteins and low-density lipoproteins, is increased, and total cholesterol and in particular high-density-lipoprotein cholesterol are decreased. The major cause of lipid abnormalities in ARF is an impairment of lipolysis. Fat particles of artificial lipid emulsions for parenteral nutrition are degraded similarly to endogenous very-low-density lipoproteins and thus, impaired lipolysis in ARF retards also elimination of intravenously infused lipids containing both long-chain triglycerides and medium-chain triglycerides.

**Protein and Amino Acid Metabolism/Protein Requirements in ARF**

The hallmark of metabolic alterations in ARF is activation of protein catabolism with excessive release of amino acids from skeletal muscle and sustained negative nitrogen balance. Muscular protein degradation and amino acid oxidation is stimulated; hepatic extraction of amino acids from the circulation, gluconeogenesis, and ureagenesis all are increased. In the liver, protein synthesis and secretion of acute-phase proteins is stimulated. As a consequence, imbalances in amino acid pools in plasma and in the intracellular compartment occur in ARF and the use of amino acids is altered; the clearance of most amino acids is enhanced.

The causes of hypercatabolism in ARF are complex and manifold and present a combination of unspecific mechanisms induced by the acute disease process and the underlying illness/associated complications, and of specific effects induced by the acute loss of renal function and by the type and intensity of renal replacement therapy (Table 1). The dominat-
ing mechanism is the stimulation of hepatic gluconeogenesis from amino acids, which, in contrast to both healthy subjects and patients with chronic renal failure (CRF), can be decreased but not halted by exogenous substrate supply.\(^5\) A major stimulus of muscle protein catabolism in ARF is insulin resistance. Moreover, acidosis was identified as an important factor in mediating muscular protein breakdown.\(^12\)

Several additional catabolic factors are operative in ARF. The secretion of catabolic hormones, hyperparathyroidism, suppression and/or decreased sensitivity of growth factors, and the release of proteases from activated leucocytes all can stimulate protein breakdown. Moreover, inflammatory mediators such as tumor necrosis factor-\(\alpha\) and interleukins stimulate hypercatabolism. In addition, renal replacement therapy can stimulate protein catabolism. Last but not least, inadequate nutrition contributes to the loss of lean body mass in ARF. Starvation can augment the catabolic response of ARF, and malnutrition was identified a major determinant of morbidity and mortality in ARF.\(^13\)

### Table 1. Factors Contributing to Protein Catabolism in Acute Renal Failure

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Impairment of metabolic functions by uremic toxins</td>
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<tr>
<td>Endocrine factors</td>
<td></td>
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<tr>
<td>Insulin resistance</td>
<td></td>
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<tr>
<td>Increased secretion of catabolic hormones (catecholamines, glucagon, glucocorticoids)</td>
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</tr>
<tr>
<td>Hyperparathyroidism</td>
<td></td>
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<tr>
<td>Suppression of release/resistance to growth factors</td>
<td></td>
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<tr>
<td>Acidosis</td>
<td></td>
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<tr>
<td>Acute phase reaction—systemic inflammatory response syndrome (activation of cytokine network)</td>
<td></td>
</tr>
<tr>
<td>Release of proteases</td>
<td></td>
</tr>
<tr>
<td>Inadequate supply of nutritional substrates</td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
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<tr>
<td>Loss of nutritional substrates</td>
<td></td>
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<tr>
<td>Activation of protein catabolism by artificial membranes</td>
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</tbody>
</table>

Serum levels of water-soluble vitamins usually are low in ARF patients mainly because of losses induced by renal replacement therapy, and thus requirements are increased in patients with ARF. An exception is ascorbic acid: as a precursor of oxalic acid, the intake should be kept below 250 mg/day because any excessive supply may precipitate secondary oxalosis.

As in CRF, vitamin D activation and plasma levels of 25(OH) vitamin D3 and 1,25-(OH) vitamin D3 are severely depressed in ARF.\(^17\) In contrast to CRF, serum levels of vitamin A and vitamin E are decreased in patients with ARF; vitamin K levels, however, are normal or even elevated.

Many of the findings on trace element metabolism in ARF represent unspecific alterations within the spectrum of “acute-phase reaction” and do not necessarily reflect specific effects induced by ARF. However, selenium concentrations in plasma and erythrocytes are profoundly decreased in patients with ARF.\(^18\) In critically ill patients, selenium replacement improved clinical outcome and reduced the incidence of ARF patients requiring renal replacement therapy (Fig 1).\(^19\)

Several micronutrients are important factors of the organism’s defense mechanisms against oxygen free radical induced injury. A profound de-
pression in antioxidant status has been documented in patients with ARF.18

**Metabolic Impact of Extracorporeal Therapy**

The impact of renal replacement therapy on metabolism is manifold. Several water-soluble substances, such as amino acids, vitamins, and carnitine, are lost during hemodialysis. Protein catabolism is caused not only by amino acid losses but also by activation of protein breakdown. Moreover, it has been suggested that generation of reactive oxygen species is augmented during treatment.

Recently, CRRT such as continuous hemofiltration and/or continuous hemodialysis have gained wide application in the management of critically ill patients with ARF. The metabolic consequences of these modalities may become especially relevant because of the continuous mode of therapy and associated high fluid turnover.20

**Nutrient Administration**

**Patient Selection**

In clinical practice, it has proved useful to distinguish 3 groups of ARF patients based on the extent of protein catabolism/severity of underlying disease and the resulting levels of dietary requirements (Table 2).2

Group 1 includes patients without excess catabolism. ARF is usually caused by nephrotoxins. These patients rarely will present major nutritional problems, and in most cases they can be fed orally and the prognosis is excellent.

Group 2 consists of patients with moderate hypercatabolism and frequently suffer from complications such as infections and peritonitis. Tube feeding and/or intravenous nutrition are generally required, and dialysis/CRRT may become necessary.

Group 3 are patients in whom ARF occurs in association with severe trauma, burns, or sepsis in the context of multiple organ failure syndrome. Treatment is complex and includes enteral and/or parenteral nutrition, hemodialysis or CRRT, plus blood pressure and ventilatory support. In these patients, in addition to the severity of the underlying illness, ARF is a major independent contributor to the poor prognosis.1

**Oral Feeding**

In all patients who can tolerate them, oral feedings should be used, but usually this will be restricted to nonhypercatabolic patients (group 1). Initially, 40 g of high-quality protein per day is given (0.6 g/kg body weight/day) and subsequently is gradually increased to 0.8 g/kg body weight/day as long as the blood urea nitrogen remains below 100 mg/dL. For patients treated with hemodialysis/peritoneal dialysis, protein intake should be increased to 1.0 to 1.4 g/kg/day. A supplement of water-soluble vitamins is recommended.

**Enteral Nutrition (Tube Feeding)**

Enteral nutrition has become the standard modality of nutritional support in critically ill patients and also in patients with ARF.21 Among the multiple advantages of enteral nutrition the most important is the fact that provision of even small amounts of luminal nutrients helps to maintain gastrointestinal functions, especially the barrier function of the intestinal mucosa. Moreover, enteral nutrition might exert specific advantages
in ARF. In experimental ARF, enteral nutrition can augment renal plasma flow and improve renal function.\textsuperscript{22} Enteral nutrition was a factor associated with an improved prognosis in patients with ARF.\textsuperscript{1,15}

However, few systematic studies on enteral nutrition have been conducted in patients with ARF. In the largest study to date, nutritional effects, feasibility, and tolerance of enteral nutrition using either a conventional diet or a preparation adapted to the metabolic needs of hemodialysis patients was performed in 182 patients with ARF.\textsuperscript{23} Side effects of enteral nutrient supply were higher in ARF patients as compared with patients with normal renal function, but in general enteral nutrition was safe and effective.

### Enteral formulas

Essentially, 3 types of enteral formulas can be used in ARF patients, but none of these diets have been developed specifically for nutrition in ARF.\textsuperscript{21}

Elemental powder diets. These formulas conform to the concept of a low–protein diet supplemented with essential amino acids in CRF. These diets are not complete and should be replaced by more complete ready-to-use liquid products.

Standard enteral formulas designed for nonuremic patients. In many intensive-care patients with ARF, standard enteral formulas are used. Disadvantages are the amount and type of protein and the high content of electrolytes. Whether diets enriched with specific substrates such as glutamine, arginine, nucleotides or ω-3 fatty acids (“immunonutrition”) might exert beneficial effects in patients with ARF remains to be shown.

Specific enteral formulas adapted to the metabolic alterations of uremia. Ready-to-use liquid diets adapted to the nutrient requirements of patients on regular hemodialysis therapy for the moment present the most reasonable approach in enteral nutrition of

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**Table 2. Patient Classification and Nutrient Requirements in Patients With ARF**

<table>
<thead>
<tr>
<th>Extent of Catabolism</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess urea appearance above N intake (g)</td>
<td>&gt;5</td>
<td>5–10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Clinical setting (examples)</td>
<td>Drug toxicity</td>
<td>Elective surgery +/− infection</td>
<td>Sepsis, ARDS, MODS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>20</td>
<td>60</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Dialysis/CRRT, frequency</td>
<td>Rare</td>
<td>As needed</td>
<td>Frequent</td>
</tr>
<tr>
<td>Route of nutrient administration</td>
<td>Oral</td>
<td>Enteral and/or parenteral</td>
<td>Enteral and/or parenteral</td>
</tr>
<tr>
<td>Energy recommendations (kcal/kg body weight/day)</td>
<td>20-25</td>
<td>20-25</td>
<td>25-30</td>
</tr>
<tr>
<td>Energy substrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (g/kg body weight/day)</td>
<td>3.0-5.0</td>
<td>3.0-5.0</td>
<td>3.0-5.0</td>
</tr>
<tr>
<td>Fat (g/kg/body weight/day)</td>
<td>0.6-1.0</td>
<td>0.8-1.2</td>
<td></td>
</tr>
<tr>
<td>Amino acids/protein (g/kg/day)</td>
<td>0.6-1.0</td>
<td>0.8-1.2</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>EAA (+NEAA)</td>
<td>EAA + NEAA</td>
<td>EAA + NEAA</td>
<td></td>
</tr>
</tbody>
</table>

**Nutrients used**

<table>
<thead>
<tr>
<th>Oral/enteral</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>Enteral formulas</td>
</tr>
<tr>
<td>Glucose 50%-70%</td>
<td>Glucose 50%-70%</td>
</tr>
<tr>
<td>Lipids 10%-20%</td>
<td>Lipids 10%-20%</td>
</tr>
<tr>
<td>AA 6.5%-10%*</td>
<td>AA 6.5%-10%*</td>
</tr>
<tr>
<td>Micronutrients†</td>
<td>Micronutrients†</td>
</tr>
</tbody>
</table>

**Abbreviations:** N, nitrogen; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; CRRT, continuous renal replacement therapy; EAA, essential amino acids; NEAA, nonessential amino acids; AA, amino acid solution.

*General or special “nephro” solutions (EAA + specific NEAA).
†Multivitamin and multi–trace element preparations.
hypercatabolic intensive-care patients with ARF.23

Parenteral Nutrition

In the critically ill patient with ARF it is frequently impossible to cover nutrient requirements exclusively by the enteral route alone, and supplementary or even total parenteral nutrition may become necessary.

Composition of Parenteral Nutrition Solution

Components of parenteral nutrition solution are discussed below.

Glucose. Glucose should be used as the main energy substrate. In contrast to earlier recommendations, glucose intake must be restricted to <3 to 5 g/kg body weight/day because higher intakes are not used for energy but will promote lipogenesis with fatty infiltration of the liver, excessive carbon dioxide production, immunocompetence impairment. It is important to note that because glucose tolerance is decreased in ARF, insulin is frequently necessary to maintain normoglycemia. By providing a portion of the energy by lipid emulsions, the risk of developing hyperglycemia can be reduced.

Lipid emulsions. Changes in lipid metabolism associated with ARF (vide supra) should not prevent the use of lipid emulsions. Instead, the amount infused should be adjusted to meet the patient’s capacity to utilize lipids. Usually, 1 g fat/kg body weight/day will not increase plasma triglycerides substantially. Whether lipid emulsions with a lower content of polyunsaturated fatty acids to reduce potential proinflammatory side effects should be preferred remains to be shown.

Amino acid solutions. Three types of amino acid solutions for parenteral nutrition in patients with ARF have been used: exclusively essential amino acids (EAA), standard solutions of EAA plus non-essential amino acids (NEAA), and specifically designed “nephro” solutions of adapted proportions of EAA and specific NEAA that might become conditionally essential in ARF. The use of solutions of EAA alone was based on principles established for treating CRF patients with a low-protein diet and an EAA supplement. These solutions should no longer be used because they are incomplete (several amino acids designated as NEAA such as histidine, arginine, tyrosine, serine, and cysteine may become indispensable in ARF patients) and have an unbalanced composition.2 Thus, solutions including both EAA and NEAA in standard proportions or in special proportions (nephro solutions) should be used in patients with ARF. Because of the low water solubility of tyrosine, dipeptides containing tyrosine (such as glycyl-tyrosine) are contained in modern nephro solutions.2,24 Recently, it was suggested that glutamine exerts important metabolic functions in catabolic patients. Glutamine exerts beneficial effects on renal function and can improve survival in critically ill patients.25 In a post hoc analysis, this was most pronounced in patients with ARF (4 of 24 survivors without, 14 of 23 with glutamine, P < .02). Because free glutamine is not stable in aqueous solutions, glutamine-containing dipeptides are used as a glutamine source in parenteral nutrition.

Renal Failure Fluid

Standard solutions with amino acids, glucose, and lipids contained in a single bag are available (“all in one” solutions, Table 3). As required, vitamins, trace elements, and electrolytes can be added to these solutions. To ensure maximal nutrient use and to avoid metabolic derangements, the infusion must be started at a low rate (providing about 50% of requirements) and increased gradually over several days.

Complications of Nutritional Support

Technical problems and infectious complications originating from central venous catheters or enteral feeding tubes, metabolic complications of artificial nutrition, and gastrointestinal side effects of enteral nutrition are similar in ARF patients and in nonuremic subjects. However, metabolic complications are far more pronounced and occur more frequently in ARF because the utilization of various nutrients is impaired and the tolerance to electrolytes and volume load is limited. By gradually increasing the infusion rate and avoiding any infusion above requirements, many
side effects can be minimized. Nutrition therapy must be more closely monitored in patients with ARF than with other disease states.

**Conclusion**

The patient with ARF certainly continues to present one of the most challenging problems in clinical nutrition. Nutritional support must be viewed as a cornerstone in the treatment of patients with ARF, a specific type of metabolic intervention that cannot be separated from the adequacy of renal replacement therapy and fluid and electrolyte management, respectively. Nutritional therapy must leave a merely quantitatively oriented approach in covering nitrogen and energy requirements, and must move toward a more qualitative type of metabolic support integrating interventions aimed at modulating the inflammatory state, the oxygen radical scavenger system, and immunocompetence and at taking advantage of specific pharmacologic effects of various nutrients. A reduction of the distressingly high mortality rate of patients with ARF will largely depend on further improvements in metabolic care.

**References**


