Abstract: ARF is a major co-morbidity in patients with critical illness. Metabolic derangement with hypercatabolism is characteristic of these patients who are highly susceptible to nutritional depletion. Negative nitrogen balance driven by multiple factors involved in metabolic imbalance, exacerbates malnutrition risk. The priority of nutrition feeding is to consider the complications associated with ARF such as hyperglycaemia, hypertriglyceridaemia, and fluid and electrolyte imbalance. An additional consideration will be the derangement in nutrient balance when renal replacement therapy is instituted for oliguric ARF patients. Dialysis modalities such as haemodialysis, peritoneal dialysis and continuous renal replacement therapy affect the prescription of calories, carbohydrate, protein and micronutrients. Artificial nutrition support is strongly advocated for ARF patients who are severely catabolic and an algorithm is provided for parenteral or enteral feeding options in relation to the presence or absence of oliguria and gastrointestinal function. This review presents a rationale for approaching nutritional therapy for ARF patients with critical illness.

Keywords: ARF, oliguria, hypercatabolism, negative nitrogen balance, dialysis, nutrition support.

Introduction

Acute renal failure (ARF) is the most prevalent co-morbidity in critical illness, and it’s leading cause, tubular necrosis, accounts for 76% of Intensive Care Unit (ICU) patients (1,2). Further, the associated mortality rate ranges between 50 to 90% with complications of trauma, shock or sepsis (3,4). These are patients characterized by a sudden drop in glomerular filtration rate (GFR), build up of nitrogenous waste products and failure of the kidney to manage electrolytes, pH and water. On this basis, these patients are categorized as Group III patients experiencing severe catabolism (5). Such patients have a markedly negative nitrogen (N\textsubscript{2}) balance, suggesting optimal nutrient feeding is required. The challenge in patients presenting with negative N\textsubscript{2} balance is-Will providing optimal nutritional feeding improve prognosis in ARF patients? This question is very difficult to answer as no reported literature is available measuring the true effect of (artificial) nutrition on survival, clinical status, rate of complications, hypermetabolism, nutritional status and recovery of renal function (6,7). Of note, pre-existing malnutrition, prevalent in ARF patients at the time of hospital admission, increases the likelihood of mortality, complications and health care costs (8).

Metabolic Considerations

ARF in ICU is not an isolated organ failure but a component of complex metabolic changes imposed by multiple organ failure (9,10). This multiple sequelae affects clinical course leading to the accumulation of urea and other uremic toxins. Mineral and electrolyte problems - hyperkalemia, hyperphosphatemia are also linked to metabolic acidosis.

A. Protein-energy malnutrition

The background of malnutrition in ARF is unique to the stress induced by associated critical illness. Multifactorial metabolic changes induce negative N\textsubscript{2} balance which accelerates with severe hypercatabolism (11). N\textsubscript{2} imbalance can be attributed to any one or combination of the following factors (6,12,13):

- Endocrine imbalance- hypersecretion of glucagon, catecholamines, cortisol, parathormone, insulin resistance
- Metabolic acidosis
- Imbalance between proteases and antiproteases

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In dialysis patients, the metabolism of amino acids is altered due to hypermetabolic states such as trauma, burns, sepsis, shock, or multiple organ distress syndrome (MODS). Hypermetabolic events lead to a negative nitrogen balance with inefficient reutilization of muscle proteins. The normal pattern of utilization of a few essential amino acids (lysine, methionine, and threonine) to drive amino acid metabolism is no longer enough to supply this demand. Alterations in intracellular and extracellular amino acid pools and in the utilization of exogenous AAs (diet) occur. Non-essential amino acids (NEAA) now become conditionally essential to drive the greater demand for amino acid substrates.

With negative N balance there is inefficient reutilization of muscle proteins (17, 19). The normal pattern of utilization of a few essential amino acids (lysine, methionine, and threonine) to drive amino acid metabolism is no longer enough to supply this demand. Alterations in intracellular and extracellular amino acid pools and in the utilization of exogenous AAs (diet) occur. Non-essential amino acids (NEAA) now become conditionally essential to drive the greater demand for amino acid substrates [see Table 1].

### Table 1: Amino acid classes in human nutrition

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysine</td>
<td>Essential</td>
</tr>
<tr>
<td>Methionine</td>
<td>amino acids</td>
</tr>
<tr>
<td>Threonine</td>
<td>(EAA)</td>
</tr>
<tr>
<td>Leucine</td>
<td>Branched chain</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>amino acids</td>
</tr>
<tr>
<td>Valine</td>
<td>(BCAA)</td>
</tr>
<tr>
<td>Trpophane</td>
<td>Aromatic</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>amino acids</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>(AAA)</td>
</tr>
<tr>
<td>Glycine</td>
<td>Non-essential</td>
</tr>
<tr>
<td>Proline</td>
<td>amino acids</td>
</tr>
<tr>
<td>Cystine</td>
<td>(NEAA)</td>
</tr>
<tr>
<td>Serine</td>
<td></td>
</tr>
<tr>
<td>Alanine</td>
<td></td>
</tr>
<tr>
<td>Aspartic acid</td>
<td></td>
</tr>
<tr>
<td>Glutamic acid</td>
<td></td>
</tr>
<tr>
<td>Arginine</td>
<td>Semi essential</td>
</tr>
<tr>
<td>Histidine</td>
<td>amino acids (SEAA)</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Conditionally essential amino acids (CEAA)</td>
</tr>
</tbody>
</table>

### B. Hyperglycaemia

Conditions of elevated blood glucose levels develop in ARF due to both hypercatabolism and rising BUN levels (21-24). Hyperglycaemia (>300mg/dL) is a many-fold result of...
disordered blood homeostasis. It is an aggravated exogenous overload from decreased substrate utilization resulting from peripheral insulin resistance. The greater role of the kidney in the development, maintenance and resolution of hyperglycaemia in critical illness is suggested from emerging evidence (23,25).

Hyperglycaemia promotes hepatic gluconeogenesis which utilizes protein as an alternate calorie source as well as increased oxidation of essential amino acids (23). It is thought to play an important role in aggravating inflammatory response by enhancing the production of free radicals and cytokines (IL1, IL6 and TNF) (21).

**C. Hypertriglyceridaemia**

Alterations in lipid metabolism are manifested and typified by hypertriglyceridaemia due to an inhibition of lipolysis by rising BUN levels (10). The postprandial clearance of long and medium chain triglycerides are typically halved during acute renal failure (5).

**D. Micronutrient abnormalities**

In ARF, there is limited excretion of most trace elements excepting zinc, manganese, copper, selenium and chromium (6). The latter minerals are excreted via the GI tract route. Increased excretion of N₂ promotes electrolyte imbalance by increasing sodium retention and excretion of magnesium and calcium.

Hypoxia with fat-soluble vitamin A can occur due to retention in renal failure (7,25). In contrast, decreased plasma concentrations of water-soluble vitamin C are associated with the systemic inflammatory response induced by uraemia or dialysis (5). The vitamin D metabolite (1,25 OH-cholecalciferol) can be rapidly depleted with renal dysfunction despite reduced rates of calcitriol degradation (26).

Impaired excretion of potassium and phosphorous cause hyperkalemia and hyperphosphataemia, which can be further aggravated by acidosis (7). However, risk of hyperphosphatemia and hypokalemia may develop from extracellular-to-intracellular shifts upon starting dialysis therapy, or in the malnourished patient or overfeeding upon starting nutrition support (7).

**E. Renal Replacement Therapy (RRT)**

The projected need for dialysis involving oliguric ARF patients (<400ml/24hr) is 85% whilst it is 30 to 40% in non-oliguria (urine volume >400ml/24hr) (27). Dialysis modalities include intermittent haemodialysis (IHD), peritoneal dialysis (PD) and continuous renal replacement therapy (CRRT). CRRT options use either arteriovenous (AV) or venovenous (VV) routes with hemofiltration (H), hemodialysis (HD) or hemodiafiltration (HDF) techniques. Either continuous (C) or intermittent (I) PD constitutes the mainstay of therapy in developing countries and for paediatric patients (28,29). Modality choice will depend on the severity of underlying illness, haemodynamic status, fluid requirements especially with oliguria or anuria, hypercatabolic stress and contraindications for use (30). In a haemodynamically unstable patient with oliguria requiring a high fluid turnover, CRRT via the venovenous route is the modality of choice (5,31). This makes it easier in planning nutritional support.

Dialysis choice bears some implications on the prescription of calories, carbohydrate and protein as summarized in Table 2 (32-41). Lipid administration is not affected. Other effects are:

- Water-soluble vitamins are significantly lost through dialysis particularly vitamins C, B6 and folate (42). Therefore twice their daily recommendation should be given. However vitamin C supplementation should not exceed 200mg/day in view of secondary oxalosis (43).
- Fat-soluble vitamins and trace elements are not significantly affected by ultrafiltration and their provision should meet routine daily requirements in view of potential toxicity (42,43).
- Magnesium, calcium and zinc losses during CRRT are associated with increased nitrogen loss (44)
- Phosphate losses occur from across membrane and intracellular shifts, resulting in hypophosphataemia (7).

**Primary Goals of Nutrition Support**

The priority of nutrition feeding is to consider the metabolic derangement associated with ARF in addition to the underlying disease process. An additional consideration will be the derangement in nutrient balance when RRT is instituted.

1. Energy - Resting energy expenditure (REE) can be raised by trauma or sepsis by ~30%. Providing 26kcal/kg/day has been found to offset negative N balance in hypercatabolic states compared to 35kcal/kg/day (45). Where there is higher urea nitrogen appearance (UNA) and with worsening N balance, more energy may be required but rarely beyond 40kcal/kg/day (46-48).
Table 2: Dynamics of macronutrient losses or gains from RRT modalities

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Comment</th>
<th>HD</th>
<th>PD</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose losses (34,35)</td>
<td>With glucose-free replacement fluids</td>
<td>Negligible</td>
<td>-</td>
<td>Lactate-based fluids in CRRT provide 300-500 kcal/day depending on the rate and site of fluid infusion (pre-or post-filter)</td>
</tr>
<tr>
<td>Calorie gains from replacement fluids (33-35)</td>
<td>Calories should be accounted in total nutritional prescription</td>
<td>-</td>
<td>Lactate-based provide about 100kcal/day.</td>
<td>Significant without adequate warming of equipment for blood or replacement fluids. Calorie loss may be as high as 1500kcal/day</td>
</tr>
<tr>
<td>Heat loss (34)</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dextrose absorption (33-38)</td>
<td>Carbohydrate absorption from dextrose-containing replacement fluids are negligible in 0.1 to 0.15% concentrations but become significant with 1.5%, 2.5% or even 4.25% concentrations. Calories should be accounted from the total caloric requirement of the patient. [1g dextrose provides 3.4kcal].</td>
<td>With PD about 180g of glucose or an equivalent of 620kcal can be absorbed per day depending on the concentration and volume of the PD solution. On IPD (60 min cycle) with 1.5% exchanges, an equivalent of 830 kcal equivalent of glucose per 24hr is absorbed. If 4.25% glucose is used in every 3rd bag, then 1230 kcal equivalent of glucose will be absorbed.</td>
<td>Glucose uptake depends on the dextrose load because of the glucose concentration gradient: 1.5% dextrose- 43% uptake2.5% dextrose- 45% uptake4.25% dextrose- 80% uptake</td>
<td></td>
</tr>
<tr>
<td>Nitrogen losses (36,37,55,56)</td>
<td>Protein catabolism increases with dialysis and is affected by the type, duration and intensity of modality. AA losses amount to 5 to 8g on a low flux dialyzer or 30% more on a high-flux membrane per IHD session IPD - 5 to 17g protein loss per session. CPD - 6g protein per session on CPD. Protein loss increases with peritonitis.</td>
<td>IPD - 5 to 17g protein loss per session.</td>
<td>Through CRRT, AA losses approximate 15g/day.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HD - haemodialysis; PD - Peritoneal dialysis; CRRT - continuous renal replacement therapy; IPD - intermittent peritoneal dialysis; CPD - continuous peritoneal dialysis; AA - amino acids
A greater calorie prescription may achieve a positive N₂ balance but will increase risk for nutrition-related side effects. Fiaccadori et al (2005) demonstrated this in an open label crossover study with 10 ARF patients on a caloric provision of either 30 or 40 kcal/kg/BW (45). Nitrogen was provided at 0.25g/kg/day for both regimes. These were patients receiving TPN and on RRT.

Energy calculations are best based on the Harris-Benedict equation as an estimate of basal energy expenditure (BEE) can be calculated (26,47,48). A further advantage is that EEE can be corrected for stress conditions. A factor of 1.3 for a patient without stress or 1.5-1.7 for hypermetabolic conditions can be used (26). To avoid overfeeding metabolically unstable patients who are likely to be overhydrated or with edema, dry weight should be used in calculations.

The amount and type of energy substrates used in nutrition support becomes critical in the presence of hyperglycaemia and hypertriglyceridaemia (5,6,10). Lipids are limited to 20-25% of non-protein calories (5). Lipids generate less CO₂ compared to carbohydrate, have lower osmolality, provide essential fatty acids and are a concentrated source of energy-9kcal per gram. But using either medium chain triglycerides or the longer chain fatty acids will not offer any advantage in reducing hypertriglyceridaemia (5).

Carbohydrate as a source of glucose becomes critical in managing hyperglycemia. The amount should be provided according to metabolic tolerance. Glucose provision is best restricted to 3 to 5g/kg BW/day (5). The use of insulin may be required to achieve this objective (5,21).

2. Protein- N₂ balance is the criterion for adequate protein intake unlike other nutrients' adequacy which is based on the treatment or prevention of a specific disease state. In acutely ill hypercatabolic patients with ARF, positive N₂ balance is achieved only if protein intake is greater than 1g/kg/day and it is further improved by a relatively lower energy intake of 26kcal/kg/day (46). Since dialysis procedures are associated with loss of amino acids and/or proteins, especially with high flux dialysers, an additional 0.2g/kg/day is required (6). With more aggressive haemofiltration, N₂ balance has been shown to improve with 2.5g vs 1.2g/kg/day (6).

No optimal AA composition has been defined. However the proportion of AA composition is different in uremia compared to non-uremic patients. Since non-essential AAs become conditional in critical illness- arginine, tyrosine, cysteine, serine- a combination of NEAA + EAA should be provided (47,48). A 3 or 4:1 proportion is recognized as favourable compared to 1:1 formulations (4). There is no evidence for the use of branched chain amino acids (26).

**Providing Nutrition Support**

**When should nutritional feeding be initiated?**
Starting nutrition support for the ARF patient is not straightforward. This is because the clinical diagnosis of ARF lacks a uniform definition that is commonly applicable to patients in ICU (2). ARF diagnosis relies on changes in serum creatinine (rise by 0.5mg/dL or 40μmol/L) and urine output (50% fall in GFR). This is neither sensitive nor specific as the response variable to the disease is individual (susceptibility) and dependent on baseline serum creatinine levels and the presence or absence of proteinuria (27,50). The decision to initiate nutrition support in ARF is further complicated by medical therapies aimed at preventing ARF (1-2 days), limiting the extension phase (3-4 days) and/or treating established ARF (1-6 days) (51). At each one of these phases if a decision is made to reduce uraemia, then either nil-by-mouth or conservative practices in nutrition feeding may be options in nutritional management. Nutrient optimisation to correct negative N₂ balance may then be initiated in the recovery phase of ARF (after 6 days).

An Expert Consensus Group of the European Society of Parenteral and Enteral Nutrition (ESPEN) has cautioned against commencing feeding within the first 48h after trauma (ebb phase) due to enhanced renal oxygen consumption from nutrient substrates as well as aggravating renal damage (6). In contrast, early oral feeding with conservative management is recommended for non-oliguric patients.

**How much protein should be provided?** N₂ amounts should be calibrated according to the degree of catabolism, intercurrent illness, type of treatment [conservative or dialysis] and residual renal function. Recommendations are to estimate the extent of protein catabolism from urinary nitrogen appearance (UNA) (10,26). However, an alternate practical approach is to use the presence or absence of oliguria to determine the protein prescription for nutrition feeding as recommended by the ESPEN Expert Consensus Group (6). A patient without oliguria may be managed conservatively on a low protein diet [0.55-6 g/kg BW daily] and about 50-55% of this protein should be of high biological value (HBV). This may be increased to 0.8g protein/kg BW if BUN falls below 36mmol/L. If oliguric and the patient is undergoing dialysis, a more liberal protein prescription is needed to make up dialysate...
losses (4). If PD, HD or haemofiltration is the RRT choice then providing 1.0-1.5g protein/kg BW per day will be adequate. Patients on CRRT will require 1.5-2.5g protein/kg BW daily to replace the greater dialysate losses.

Table 3: Vitamin recommendations for ARF patients*(4,5)

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>as per RDA (monitor for toxicity)</td>
</tr>
<tr>
<td>D</td>
<td>as per RDA (in the form 1,25-dihydroxycholecalciferol)</td>
</tr>
<tr>
<td>K</td>
<td>4 to 10mg/week</td>
</tr>
<tr>
<td>E</td>
<td>10 IU/day</td>
</tr>
<tr>
<td>Niacin</td>
<td>20mg/day</td>
</tr>
<tr>
<td>Thiamin</td>
<td>2mg/day</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>2mg/day</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>10mg/day</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>10mg/day</td>
</tr>
<tr>
<td>C</td>
<td>60 to 200mg/day</td>
</tr>
<tr>
<td>Biotin</td>
<td>200mg/day</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1mg/day</td>
</tr>
<tr>
<td>B12</td>
<td>3 to 4 mg/day</td>
</tr>
</tbody>
</table>

*Vitamin supplementation required for parenteral feeding option.

RDA= recommended daily requirement as per normal health.

HBV is an index of protein quality from the viewpoint of substrate utilisation in enhanced catabolic states. In protein planning, therefore, the choice of amino acid solutions is based on the content of essential amino acids (EAA) and non-essential amino acids (NEAA). An optimal ratio ranging from 2:1 to 4:1 has been suggested (6). The use of NEAA is mandatory if the protein requirement is more than 0.4-0.5g/kg/day (4). An optimal AA composition specific for uremia comprising histidine, taurine and tyrosine has also been suggested (4).

How should feeding be provided? - Either a functioning gastrointestinal (GI) tract or impaired GI motility will be important considerations in making a decision on how to effect feeding. The advantages and disadvantages of choosing either enteral (EN) or parenteral nutrition (PN) as feeding modalities have been well reviewed (11). Infectious and metabolic complications are commonly associated with PN (11). Additionally a higher risk of cardiac arrhythmias is associated with central vein catheter use (52,53). Patients are selected for PN if EN is contraindicated for 4 or more days. Severe malnutrition and hypercatabolism typify such patients adding to the risk of poor outcome (6).

Enteral nutrition, particularly tube feeding improves patient survival (54-57). However, the impact on complicated and uncomplicated ARF has not being measured. Tube feeding has been recommended by recent ESPEN guidelines whenever nutritional requirements are not adequately met orally as a means to support GI function in the critically ill (25). Aside from higher gastric residuals, nasogastric feeding has been found to be safe and effective in 182 ARF patients using either standard formula or disease specific formula (58). However although the adage ‘if the gut works use it’ advocates enteral nutrition as the preferred choice of nutrition support, it is not applicable to all ARF patients in ICU (5). Figure 2 provides an algorithm to guide nutrition feeding for the ARF patient.

Figure 2: Algorithm for deciding feeding options in ARF

Abbreviations : HD - haemodialysis; PD - Peritoneal dialysis; CVVH - continuous venovenous haemodialysis; CVVHDF - continuous venovenous hemodialfiltration; GI - gastrointestinal system.

EN product specifics

- Standard enteral formulations (polymeric) are unable to meet the higher recommendations for protein intake for ARF patients (7). Additions of modular products such as free amino acid or peptide-based supplementation are necessary to augment any nutrition support plan with these formulae.
The higher osmolality of the resultant mixture may cause intolerance.

- Available disease-specific enteral products are not justified for use in ARF. However a ready-to-use energy dense liquid formulation for maintenance haemodialysis patients high in protein and low in phosphate and electrolytes is the most reasonable product available for adaptive use in ICU hypermetabolic patients with ARF (5,7).

- Most enteral products provide sufficient electrolytes (5,7). However upon feeding commencement plasma electrolytes must be monitored to detect hypokalemia or hypophosphatemia.

**PN specifics**

- For a hypervolemic patient, volume limitations of the PN regimen will affect planning. Fluid restriction will affect the choice for substrate concentrations for dextrose (70%), amino acids (10 or 15%) and lipids (20 or 30%) (59,60). After determining the nitrogen plan for the regimen, about 50 to 70% of carbohydrates should provide non-protein calories with the remainder from lipids. Appropriate solutions can be compounded using 2-in-1 systems with a lipid co-infusion or opting for a total nutrient admixture (3-in-1). Concentrated PN feeding requires central access.

- PN bypasses the GI. Thus the physiological compensation (excretion) to achieve electrolyte and mineral homeostasis becomes limited. Provision of dialysis increases their losses. Therefore hypertoxicity or depletion status of micronutrients must be assessed if PN is indicated in feeding the ARF patient. Prescribing vitamins, minerals and electrolytes should be based on a daily review of a basic metabolic panel that includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorous and magnesium (44).

- If the medical protocol is to manipulate replacement fluids to treat electrolyte and acid-base balance, then the PN regimen must account for this (61). Alternately, if the PN regimen is expected to correct electrolyte and acid-base balance then acid-base neutrality is maintained by adjusting the chloride-to-acetate ratio of the electrolytes by 1:1.

- Incompatibility of sodium bicarbonate with acidic PN solutions results in CO₂ formation and loss of bicarbonate ions (62). Then, a higher acetate concentration is indicated with metabolic acidosis whereas more chloride and less acetate are warranted with metabolic alkalosis (62).

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- If calcium is to be added to prevent hypocalcemia, then it should be infused separately with magnesium salts as it is incompatible with bicarbonate (30).

- Infusion rate must be started at 50% of requirements and gradually increased over several days to achieve the planned regimen. This is to avoid metabolic derangements of rising BUN levels, hyperglycaemia and hypertriglyceridaemia (5).

- Tolerance for 200 to 250g dextrose in the first 24hr has been reported (63). With diabetes or hyperglycaemia, administration of dextrose should be limited to 100 to 150g on the first day. Because of the risk of hyperglycaemia, a portion of the carbohydrate requirements should be mixed with lipid emulsions (5).

- Initial provision of protein should not exceed 60 to 70g (63). Lipids should be infused over 12 to 24 hrs to minimize reticuloendothelial system dysfunction (64). Lipids can be started at 0.5g/kg/day before achieving a maximum of 1.5g/kg/day (65).

**Conclusions**

Addressing negative nitrogen balance is the priority of nutrition management in ARF patient with severe catabolism. However metabolic derangement and complications associated with it present challenges in nutrition planning. Dialysis modalities such as haemodialysis, peritoneal dialysis and continuous renal replacement therapy affect the prescription of calories, carbohydrate, protein and micronutrients. Artificial nutrition support is strongly advocated in hypercatabolic patients and an algorithm is provided for parenteral or enteral feeding options in relation to the presence or absence of oliguria and gastrointestinal function.

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