

## Module 13.1

### Nutritional Support in Acute Liver Failure

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### Learning Objectives

To understand:

- The key metabolic problems of patients with acute liver failure.
- The caveats regarding administration of amino acids and protein.
- Practical approaches to nutritional support.

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### Key Messages

- Overall approaches to nutritional support do not differ markedly from other critical illness.
- Most patients do not have malnutrition at the onset of illness.
- Patients have increased resting energy expenditure.
- Some patients may have severe hyper-aminoacidaemia contributing to hyper-ammonaemia and risk of cerebral oedema.

## **0. Introduction**

Acute Liver Failure (ALF) is a rare critical illness with an incidence in the developed world of <6 cases per million population per year. Triggered by a wide variety of toxic or infectious insults, it typically affects young adults in the absence of pre-existing Chronic Liver Disease (CLD)(1). The rapidity of development is such that most patients will not have evidence of malnutrition at the time of illness onset, though nutritional compromise may develop during the period of acute illness severity, resolution and recovery. Its rarity, severity and rapid trajectory is such that few clinical trials of any sort – including those of nutritional interventions – have been performed. Treatment is thus mainly based upon clinical observation of patients with ALF, and extrapolation from other critical illness. Despite this lack of a formal evidence base, outcomes for patients with ALF have improved markedly over recent years suggesting that the approaches adopted do have merit (2).

## **1. Pathophysiology**

Acute liver failure is defined by the presence of laboratory evidence of acute liver injury (ALI) with complicating hepatic encephalopathy (HE). In some cases, particularly those where illness onset is very rapid ('hyper-acute'), HE carries risk of development of cerebral oedema and intracranial hypertension (1). The time-course of illness is usually relatively short, either due to rapid hepatic regeneration, transplantation or early death. Nutrition support is indicated to support regeneration in patients managed with medical care alone, whilst waiting for transplantation or in the post-transplantation phase of illness.

## **2. Metabolic Response and Energy Expenditure**

The metabolic response to acute liver failure is characterized by the combined consequences of a failing liver and loss of hepatic metabolic capacity, the stress metabolism associated with critical illness and activation of a systemic inflammatory response. Under normal circumstances hepatic energy expenditure contributes 25% of whole body expenditure, but despite major loss of hepatic functional mass in ALF, the limited studies utilising indirect calorimetry suggest an overall increase in energy expenditure (3, 4). The basis for this is uncertain, but may reflect co-existent major systemic inflammatory activation.

### **2.1 Glucose Metabolism**

A principal biochemical anomaly seen in ALF is that of hypoglycaemia, reflecting loss of hepatic gluconeogenic capacity, depletion of hepatic glycogen and hyper-insulinism (5). Universal practice is for prevention of hypoglycaemia by close monitoring of blood glucose and continuous intravenous infusion of glucose (6).

### **2.2 Lipid Metabolism**

Patients with ALF have low plasma concentrations of free fatty acids with low

hepatic uptake reflecting impaired hepatic utilisation, and very low concentrations of ketone bodies reflecting absent hepatic ketogenesis (7). Loss of hepatic beta-oxidation capacity has been documented in some cases and theoretically could compromise the ability to utilise exogenously administered lipids from nutritional support or from the use of the sedative agent propofol. In practice this does not seem to be a major issue; where concern exists, particularly if high doses or prolonged treatment with propofol or parenteral nutrition (PN) is required, plasma triglyceride levels may be measured and infusions adjusted as necessary.

### **2.3 Amino Acid Metabolism**

In ALF plasma levels of amino acids are increased three- to four-fold and the pattern of amino acids is altered with a relative reduction in branched-chain amino acids and a relative increase in tryptophan, aromatic and sulphur-containing amino acids (8). There is no net elimination of amino acids in the splanchnic area, but a high rate of conversion of glutamine to ammonia and alanine (8). Urea production is reduced or absent. In brain and muscle, ammonia is reconverted to glutamine, and both produce more glutamine than can be accounted for by ammonia and amino acid uptake in these tissues, indicating a state of protein catabolism (8, 9).

Hyperammonaemia is thought to be a principal cause of HE in ALF, with a closer relation seen between its circulating concentration and HE severity than in chronic liver failure. Its aberrant cerebral metabolism may result in astrocyte swelling and potentially fatal brain oedema. A plasma ammonia concentration of  $>150 \mu\text{mol/l}$  appears to be a critical threshold, particularly if sustained (10, 11). The mechanism of development of brain oedema involves intracerebral accumulation of osmotically active glutamine and inhibition of mitochondrial function (12). The use of continuous haemofiltration as renal replacement therapy (RRT) assists in keeping the plasma ammonia below critical levels and in removing excess glutamine (13). Muscle uptake of ammonia and its conversion to glutamine represents a possible target for therapeutic augmentation, but trials in ALF of the ammonia lowering agent L-Ornithine Aspartate that is thought to act through this mechanism have not shown clinical benefit (14).

## **3. Energy, and Substrate Requirements**

### **3.1 Energy Requirements**

Resting energy expenditure is increased by 20-25% compared to the predictions of the Harris-Benedict equations (3, 4). Goals of nutritional support are determined with this taken into account as in other critical illness (15).

### **3.2 Protein Requirements**

As noted above, there is concern about the use of protein/amino acids in some patients with hyper-acute ALF and elevated arterial ammonia levels ( $>150 \mu\text{mol/l}$ ) who may be at increased risk of cerebral oedema (10). In this specific setting where

there may be short-lived but profound impairment of hepatic function, protein administration may further elevate ammonia levels and increase cerebral oedema risk. Protein delivery may be deferred in these patients for a short period only (24-48 hours) as liver function improves. When commenced, targets in the range of 0.8-1.5 g/kg/d are adopted dependent on the phase of illness, organ support requirements and concurrently measured arterial ammonia concentration. Whilst the use of renal replacement therapy (RRT) may usefully increase ammonia removal, it will also increase loss of circulating amino acids and potentially require increased protein intake (16). Any potential clinical benefit of administering supplementary branched-chain amino acids remains to be demonstrated and this strategy is not widely adopted (17).

### **3.3 Carbohydrate & Lipid Requirements**

Combinations of carbohydrate/glucose and fat/lipid should be given to cover energy needs in the amounts commonly utilised in other intensive care patients but with monitoring of triglyceride levels. Most centres aim for triglyceride levels <4 mMol/l (6). Intravenous glucose is infused at a rate of at a rate of 1.5-2.0 g kg<sup>-1</sup>day<sup>-1</sup>.

## **4. Requirements for Vitamins and Minerals**

There is no basis for specific recommendations for vitamins and minerals; the amounts commonly used in other intensive care patients should therefore be used. The frequent requirement for RRT in patients with ALF may necessitate extra supplementation of micronutrients including water soluble vitamins (16).

## **5. Route of Feeding**

In the majority of patients with ALF it is practical and safe to use enteral nutrition (EN), and in most cases formulae can be delivered in amounts comparable to other critical illness. In other critically patients who require nutrition support therapy, PN carries no clear advantage over EN and may increase infectious complications: the same may be the case in ALF (15). A recent survey of nutritional practice in ALF suggests that most centres now use EN as a first line route of support (17).

## **6. Summary**

Patients with acute liver failure have a relatively short course of disease, either because of rapid liver regeneration, transplantation or early death. Most often their illness has developed in the setting of a relatively well preserved nutritional state. Nutrition support is indicated to support hepatic regeneration, whilst waiting for transplantation or in the post-transplantation phase of illness. Lack of physiological and trial data means that most centres adopt standard approaches taken in other critically ill patient groups, but with close monitoring and modulation of blood glucose, ammonia and triglyceride levels.

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