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ESPEN Guidelines on Parenteral Nutrition: Hepatology

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SUMMARY

Parenteral nutrition (PN) offers the possibility to increase or to ensure nutrient intake in patients, in whom sufficient nutrition by oral or enteral alone is insufficient or impossible. Complementary to the ESPEN guideline on enteral nutrition of liver disease (LD) patients the present guideline is intended to give evidence-based recommendations for the use of PN in LD. For this purpose three paradigm conditions of LD were chosen: alcoholic steatohepatitis (ASH), liver cirrhosis and acute liver failure. The guideline was developed by an interdisciplinary expert group in accordance with officially accepted standards and is based on all relevant publications since 1985. The guideline was presented on the ESPEN website and visitors' criticism and suggestions were welcome and included in the final revision. PN improves nutritional state and liver function in malnourished patients with ASH. PN is safe and improves mental state in patients with cirrhosis and severe HE. Perioperative (including liver transplantation) PN is safe and reduces the rate of complications. In acute liver failure PN is a safe second-line option to adequately feed patients in whom enteral nutrition is insufficient or impossible.

Summary of statements: Alcoholic Steatohepatitis

Subject	Recommendations	Grade	Number
General	Use simple bedside methods such as the Subjective Global Assessment (SGA) or anthropometry to identify patients at risk of undernutrition.	C	1
	Start PN immediately in moderately or severely malnourished ASH patients, who cannot be fed sufficiently either orally or enterally.	A	1
	Give i.v. glucose (2–3 g kg^{-1} d^{-1}) when patients have to abstain from food for more than 12 h.	C	1
	Give PN when the fasting period lasts longer than 72 h.	C	1
Energy	Provide energy to cover 1.3 × REE	C	2
	Give glucose to cover 50–60 % of non-protein energy requirements.	C	3
	Use lipid emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure soybean oil emulsions.	C	3
Amino acids	Provide amino acids at 1.2–1.5 g kg^{-1} d^{-1}.	C	3
Micronutrients	Give water soluble vitamins and trace elements daily from the first day of PN.	C	3
	Administer vitamin B1 prior to starting glucose infusion to reduce the risk of Wernicke's encephalopathy.	C	3
Monitoring	Employ repeat blood sugar determinations in order to detect hypoglycemia and to avoid PN related hyperglycemia.	C	6
	Monitor phosphate, potassium and magnesium levels when refeeding malnourished patients.	C	3

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Summary of statements: Liver Cirrhosis			
Subject	**Recommendations**	**Grade**	**Number**
General	Use simple bedside methods such as the Subjective Global Assessment (SGA) or anthropometry to identify patients at risk of undernutrition.	C	4
	Start PN immediately in moderately or severely malnourished cirrhotic patients, who cannot be fed sufficiently either orally or enterally.	A	4
	Give i.v. glucose (2–3 g kg^{-1} d^{-1}) when patients have to abstain from food for more than 12 h.	C	4
	Give PN when the fasting period lasts longer than 72 h.	C	4
	Consider PN in patients with unprotected airways and encephalopathy when cough and swallow reflexes are compromised.	C	4
	Use early postoperative PN if patients cannot be nourished sufficiently by either oral or enteral route.	A	4
	After liver transplantation, use early postoperative nutrition; PN is second choice to EN.	C	4
Energy	Provide energy to cover 1.3 x REE	C	5
	Give glucose to cover 50 % - 60 % of non-protein energy requirements.	C	6
	Reduce glucose infusion rate to 2–3 g kg^{-1} d^{-1} in case of hyperglycemia and use consider the use of i.v. insulin.	C	6
	Use lipid emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure soybean oil emulsions.	C	6
Amino acids	Provide amino acids at 1.2–1.5 g kg^{-1} d^{-1}.	C	7
	In encephalopathy III° or IV°, consider the use of solutions rich in BCAA and low in AAA, methionine and tryptophane.	A	7
Micronutrients	Give water soluble vitamins and trace elements daily from the first day of PN.	C	8
	In alcoholic liver disease, administer vitamin B1 prior to starting glucose infusion to reduce the risk of Wernicke's encephalopathy.	C	3, 8
Monitoring	Employ repeat blood sugar determinations in order to avoid PN related hyperglycemia.	A	6
	Monitor phosphate, potassium and magnesium levels when refeeding malnourished patients.	C	8

Summary of statements: Acute Liver Failure			
Subject	**Recommendations**	**Grade**	**Number**
General	Commence artificial nutrition when patient is unlikely to resume normal oral nutrition within the next 5–7 days.	C	9
	Use PN when patients cannot be fed adequately by EN.	C	9
Energy	Provide energy to cover 1.3 × REE.	C	10
	Consider using indirect calorimetry to measure individual energy expenditure.	C	10
	Give i.v. glucose (2–3 g kg^{-1} d^{-1}) for prophylaxis or treatment of hypoglycaemia.	C	11
	In case of hyperglycaemia, reduce glucose infusion rate to 2–3 g kg^{-1} d^{-1} and consider the use of i.v. insulin.	C	11, 6
	Consider using lipid (0.8 – 1.2 g kg^{-1} d^{-1}) together with glucose to cover energy needs in the presence of insulin resistance.	C	11
Amino acids	In acute or subacute liver failure, provide amino acids at 0.8–1.2 g kg^{-1} d^{-1}.	C	11
Monitoring	Employ repeat blood sugar determinations in order to detect hypoglycaemia and to avoid PN related hyperglycaemia.	C	11
	Employ repeat blood ammonia determinations in order to adjust amino acid provision.	C	11

1. Alcoholic Steatohepatitis (ASH)

1.1. Indication and time of PN in ASH

Immediate commencement of PN is indicated in ASH patients with moderate or severe malnutrition, who cannot be fed sufficiently either orally or enterally (A).

ASH patients who can be fed sufficiently either by oral or enteral route but who have to abstain from food temporarily (including nocturnal fasting!) for more than 12 h, should be given i.v. glucose at 2-3 g kg^{-1} d^{-1} (C). When this fasting period lasts longer than 72 h total PN is required (C).

Comments: The prognostic significance of a poor nutritional state is documented for patients with ASH (III°).[1–3] Simple bedside methods like the "Subjective Global Assessment" or anthropometry are recommended to identify patients at risk.[4]

PN supplemental to oral nutrition ad libitum was studied in seven controlled trials using conventional amino acid solutions. The parenteral intake ranged from 200 to 3000 kcal d^{-1} providing 35–130 g amino acids per day while the oral intake ranged from 13 to 39 kcal kg^{-1} d^{-1}.[5–13] None of these trials showed a change in mortality; this may be due to the inclusion of patients with a low risk and only moderate disease severity. No adverse effects of increased nitrogen intake were observed but hepatic encephalopathy was graded by clinical assessment only. In the majority of trials there was an improvement in visceral proteins as a measure of the nutritional state. An improvement in liver function (galactose elimination, serum bilirubin) was also described.

In patients with cirrhosis, after an overnight fast glycogen stores are depleted and metabolic conditions are similar to prolonged starvation in healthy individuals. It has been shown that a late evening carbohydrate snack is associated with improved protein metabolism in cirrhotic patients.[14–16] Therefore, it is recommended that patients who need to be managed nil by mouth should be given glucose i.v. at a rate equal to the endogenous hepatic glucose production.

1.2. Energy intake

In practice it can safely be assumed that ASH patients have an energy requirement of 1.3 times the basal metabolic rate (C).

Comments: One study[17] showed that in ASH patients the relationship between measured and predicted resting energy expenditure was no different from healthy individuals. ASH patients did, however, show a higher energy expenditure when related to their reduced muscle mass as assessed by 24 h urinary creatinine excretion.

In cirrhotics without ascites actual body weight should be used for the calculation of the basal metabolic rate using formulae such as that proposed by Harris and Benedict. In patients with ascites the ideal weight according to body height should normally be used, despite a series of 10 patients with liver cirrhosis of whom only 4 were completely evaluated,[18] from whom it was suggested that ascites mass should not be omitted when calculating energy expenditure by use of body mass.

1.3. Nutrient intake in total PN

Carbohydrate should be given as glucose to cover 50–60 % of non-protein energy requirements (C).

Lipid should be provided using emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure

soybean oil emulsions and should cover 40–50% of non-protein energy requirements (C).

Amino acid provisions should amount to 1.2 g kg^{-1} d^{-1} in patients who are not or only moderately malnourished, and to 1.5 g kg^{-1} d^{-1} in the severely malnourished (C).

Water soluble and fat soluble vitamins as well as minerals and trace elements must be administered daily from the beginning of PN in order to cover daily requirements (C).

Comments: these recommendations are made by analogy to the use of PN in cirrhosis, which in many cases is already present in ASH patients. There are no systematic trials on the quantity and the composition of parenteral nutrient mixtures for ASH.

Compared to the traditional soy bean based LCT emulsions (n-6:n-3 = 8:1), new fat emulsions have a lower content in n-6 unsaturated fatty acids due to the admixture of MCT and/or olive oil and/or fish oil rendering them less suppressive to leukocyte and immune function and less stimulant of pro-inflammatory modulators.[19–23]

All water soluble vitamins, in particular thiamine (vitamin B1), pyridoxine (vitamin B6), nicotinamide (vitamin PP) and folic acid, and fat soluble vitamins should be administered daily in a standard TPN dosage. Due to the high risk of Wernicke's encephalopathy, vitamin B1 must be administered prior to starting i.v. glucose in alcoholic patients. Recently, high doses for both prophylaxis (250 mg i.m. daily for three to five days) and treatment (500 mg i.v. T.i.d. for 2–3 days) of Wernicke's encephalopathy have been advocated.[24] In jaundiced patients vitamin K deficiency due to cholestasis-induced fat malabsorption may require i.v. vitamin K for correction.

Trace elements should be administered daily in a standard TPN dose. In a pragmatic approach routine administration of twice the normal daily requirement of zinc ($=2 \times 5$ mg d^{-1}) is recommended. Malnourished ASH patients are at great risk of developing refeeding syndrome and additional phosphate, potassium and magnesium will be required, together with water soluble vitamins.

2. Liver cirrhosis

2.1. Indication and timing of PN in cirrhosis

Immediate commencement of PN is indicated in moderately or severely malnourished cirrhotics who cannot be nourished sufficiently by either oral or enteral route (C).

Cirrhotics who can be fed sufficiently either by the oral or enteral route but who have to abstain from food temporarily (including nocturnal fasting!) for more than 12 h should be given i.v. glucose at 2–3 g kg^{-1} d^{-1} (C). When this fasting period lasts longer than 72 h total PN is required (C).

PN should be considered in patients with unprotected airways and encephalopathy (HE) when cough and swallow reflexes are compromised (C).

Cirrhotic patients should receive early postoperative (additional) PN after surgery if they cannot be nourished sufficiently by the oral/enteral route (A).

After liver transplantation patients should receive early postoperative nutrition; PN is second choice to enteral nutrition (C).

Currently, no recommendations can be made regarding donor or organ conditioning by use of i.v. glutamine or arginine with the object of minimising ischaemia/reperfusion damage (C).

Comments: numerous descriptive studies have shown higher rates of complications and mortality in cirrhotic patients with protein malnutrition as well as reduced survival when such patients undergo liver transplantation.[25–32]

With the exception of "skid row" alcoholics both prevalence and severity of malnutrition are independent of the aetiology of liver disease[26,33,34] but do correlate positively with the severity of the illness. The prevalence of protein energy malnutrition increases from 20% in Child-Pugh class A to over 60% in class C.[33] Poor oral food intake is a predictor of an increased mortality: in trials on the efficacy of supplemental enteral nutrition, cirrhotics with the lowest spontaneous energy intake showed the highest mortality.[2,35–38] There are, however, no systematic trials on PN in cirrhotic patients without ASH.

Simple bedside methods like the "Subjective Global Assessment" or anthropometry have been shown to identify malnutrition adequately; the use of more complex scoring systems has not proved superior.[4]

In cirrhotics, after an overnight fast glycogen stores are depleted and metabolic conditions are similar to prolonged starvation in healthy individuals. It has been shown that a late evening carbohydrate snack was associated with improved protein metabolism in cirrhotic patients.[14–16] Therefore, it is recommended that patients who need to be managed nil by mouth should be given glucose i.v. at a rate equal to the endogenous hepatic glucose production.

Due to somnolence and psychomotor dysfunction oral nutrition is often insufficient even in mild encephalopathy (I°–II°).[39] Therefore, tube feeding may be required to ensure adequate nutrient provision. PN should be considered in patients with unprotected airways and advanced HE when swallow and cough reflexes are compromised. There are no systematic comparisons between enteral and parenteral nutrition in patients with cirrhosis and encephalopathy.

In malnourished cirrhosis patients, the risk of postoperative morbidity and mortality is increased after abdominal surgery.[40] After visceral surgery in cirrhotics, a lower complication rate was observed when postoperative PN was given instead of just fluid and electrolytes[41,42] (Ib).

After liver transplantation postoperative nutrition confers the advantage of shorter periods on mechanical ventilation and shorter ICU stay when compared to just fluid and electrolyte infusions[43] (Ib). In a direct comparison between PN and early enteral nutrition, both strategies proved to be equally effective with regard to the maintenance of nutritional state.[44] Fewer viral infections and improved nitrogen retention, however, were observed in patients on enteral nutrition commenced as early as 12 h after the transplantation.[45]

At present, it is uncertain, whether there is value in donor or organ conditioning by reducing ischaemia/reperfusion damage with the provision of high doses of arginine or glutamine.

2.2. Energy intake

For practical purposes it can safely be assumed that cirrhotic patients have an energy requirement of 1.3 times the basal metabolic rate (C).

Comments: on average, measured REE is of the same magnitude as energy expenditure predicted by use of formulae (Harris and Benedict, Schofield, etc.) but measured REE is higher than predicted in up to 30–35% of cirrhotic patients (hypermetabolism), and below the predicted value in 18% of the patients.[46–48] Whenever available, indirect calorimetry should be used to measure REE, since in the individual patient measured REE may differ considerably from estimated values.[49] It has been shown that hypermetabolism in cirrhosis is associated with reduced event-free survival and unfavourable outcome after transplantation[32,48] and seems to regress with improvement of body composition.[50] For the diagnosis of hypermetabolism, however, indirect calorimetry is required so

that in daily practice most clinicians cannot use this approach. Measurements of total energy expenditure in patients with cirrhosis indicate that the 24 h energy requirement of cirrhosis patients amounts to about 130% of the basal metabolic rate.[51,52] Diet-induced thermogenesis[53–55] and the energy cost of defined physical activity in stable cirrhosis patients[56–58] also show no deviation from values obtained in healthy patients. However, the spontaneous physical activity level is considerably lower in patients with cirrhosis. Obviously, the increased energy requirement in advanced illness is balanced by diminished physical activity reflecting the poor physical condition.[38,58]

In cirrhotics without ascites the actual body weight should be used for the calculation of the basal metabolic rate using formulae such as that proposed by Harris and Benedict. In patients with ascites the ideal weight according to body height should be used, despite the suggestion from a series of 10 patients with liver cirrhosis of whom only 4 were completely evaluated,[18] in which it was suggested that ascites mass should not be omitted when calculating energy expenditure by use of body mass.

Liver transplant patients on average have the same energy requirements as the majority of patients undergoing major abdominal surgery. In general, non-protein energy provision of 1.3 × REE is sufficient.[59,60] In a longitudinal study postoperative hypermetabolism peaked on day 10 after the transplantation at 124 % of the predicted basal metabolic rate.[61] By 6–12 months post-transplant there was no longer a difference between the measured and predicted basal metabolic rate.[61,62]

2.3. Nutrient intake – general

If PN is used as the exclusive form of nutrition, then the i.v. provision of all macro- and micronutrients must be ensured from the beginning of PN. (C).

Carbohydrate should be given as glucose to cover 50–60% of non-protein energy requirements (C). PN related hyperglycaemia should be avoided by all means (A). In case of hyperglycaemia glucose infusion should be reduced to 2–3 g kg^{-} d^{-1} and i.v. insulin infusion should be used (C).

Lipid should be provided using emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure soybean oil emulsions and should cover 40–50 % of non-protein energy requirements (C).

Comments: in hepatic cirrhosis the utilisation of oxidative fuels is characterised by an increased rate of lipid oxidation in the fasting state and the frequent occurrence of insulin resistance (even in Child-Pugh class A patients).[46,63–65] Insulin resistance affects skeletal muscle metabolism: glucose uptake and non-oxidative glucose disposal such as glycogen synthesis are reduced, while glucose oxidation and lactate production are normal after glucose provision.[54,66,67] Some 15–37% of patients develop overt diabetes, indicating a unfavourable prognosis.[68,69]

Ensuring euglycaemia has been shown to confer a survival and morbidity benefit to critically ill patients regardless of aetiology.[70,71] Great care, however, must be taken to avoid hypoglycaemia.[72]

In the early postoperative phase there is often a disturbance of glucose metabolism associated with insulin resistance. In this situation hyperglycaemia should be managed by reducing glucose intake because higher insulin doses are unable to increase glucose oxidation.[73] The diabetogenic potential of the immunosuppressant tacrolimus can be lowered by reducing its dose, aiming for trough levels of 3–8 ng ml^{-1} without undue risk of rejection.[74]

Only a few trials have addressed the question of the optimal composition of i.v. oxidative fuels fat and carbohydrate. Plasma clearance and oxidation of infused lipids are normal in cirrhosis patients.[75,76] Glucose and lipids have been used as metabolic fuels in a caloric ratio of 40–50:50–60 (G:L) in two trials.[77,78] One study reports that substrate and metabolite concentrations are more favourable when both glucose and lipid are infused simultaneously compared to glucose alone.[79] In hepatic transplant patients improved functioning of the reticuloendothelial system was observed when using MCT/LCT emulsions with a lower content of n-6 unsaturated fatty acids compared to pure soybean oil emulsions.[80] Compared to the traditional soybean based LCT emulsions (n-6:n-3 = 8:1), new fat emulsions have a lower content of n-6 unsaturated fatty acids due to the admixture of MCT and/or olive oil and/or fish oil rendering them less suppressive to leukocyte and immune function and less stimulant of pro-inflammatory modulators.[19–23]

2.4. Nutrient intake – amino acids

Amino acid provision should amount to 1.2 g kg^{-1} d^{-1} in compensated cirrhosis without malnutrition, and to a dose of 1.5 g kg^{-1} d^{-1} in decompensated cirrhosis with severe malnutrition (A).

A standard solution should be given in mild encephalopathy (≤II°) and a liver-adapted complete amino acid solution should be given in more severe encephalopathy (III°–IV°). Such solutions contain an increased amount of branched-chain amino acids and lower content of aromatic amino acids, methionine and tryptophan (A).

Comments: for PN in compensated cirrhosis amino acid solutions with a special "hepatic formula" composition is not required. In clinical trials studying patients with liver cirrhosis and severe encephalopathy the provision of protein or amino acids ranged from 0.6 to 1.2 g kg^{-1} d^{-1}.[81] In patients with alcoholic hepatitis or alcoholic cirrhosis with or without low-grade encephalopathy the provision ranged from 0.5 to 1.6 g kg^{-1} d^{-1}.[5–7,9–13,35–37,82] An explicit and systematic determination of the protein requirement, however, has been carried out in only a few studies. In these studies patients with stable cirrhosis were found to have an increased protein requirement leading to the recommendation of 1.2 g kg^{-1} d^{-1} contrasting with the recommended minimal intake of 0.8 g kg^{-1} d^{-1} in healthy humans.[38,51,83,84]

For PN of cirrhotics with overt HE special hepatic formula amino acid solutions high in branched-chain amino acids (35–45%) but low in tryptophan, aromatic and sulfur-containing amino acids were developed.[85–87] Such solutions help to correct the amino acid imbalance in liver cirrhosis. "Coma solutions" have been available in some countries; they contain either BCAAs alone or BCAAs and other agents supposedly effective in hepatic encephalopathy. These solutions are incomplete and thus, they can be used for the pharmacological correction of an amino acid imbalance only, but not as a nutritionally adequate nitrogen source for PN.

The efficacy of BCAAs in the treatment of HE has been studied in seven controlled but very heterogeneous trials,[88–92] the results of which are contradictory. A meta-analysis of these studies showed an improvement in mental state by the BCAA-enriched solutions, but no definite benefit in survival.[81] HE of cirrhotic patients, however, is precipitated by serious and life-threatening complications such as infection or haemorrhage which are more potent determinants of survival than HE, and therefore it is not surprising that BCAA-based PN failed to improve short term survival. Likewise, in a Cochrane analysis of seven randomised controlled trials studying 397 patients with acute HE, the parenteral BCAA

administration had a significant, positive effect on the course of HE, but not on survival.[93] Recently, it has been demonstrated that, due to the absence of isoleucine from haemoglobin, blood is a protein source of low biologic value leading to BCAA antagonism after upper gastrointestinal haemorrhage. This antagonism leads to hyperammonaemia but HE could be overcome by the infusion of just isoleucine.[94] Isoleucine solutions for i.v. infusions, however, are not commercially available. Special hepatic formula amino acid solutions (c.f. above) contain high amounts of isoleucine and of the other BCAAs, leucine and valine.

In cirrhotic patients undergoing liver resection, oesophageal transection and splenectomy or splenorenal shunt, the rate of HE was not increased when a conventional amino acid solution ($50\,g\,d^{-1}$) was used for postoperative PN instead of a BCAA-enriched amino acid solution ($40\,g\,d^{-1}$).[42] Moreover, no difference was observed between a standard and a BCAA-enriched amino acid solution after liver transplantation.[43]

After transplantation there is a considerable nitrogen loss and patients remain in negative nitrogen balance for up to 28 days[59,95] necessitating an increase in the provision of protein or amino acids. Protein or amino acid intakes of $1.0–1.5\,g\,kg^{-1}\,d^{-1}$ have been reported.[30,43] The determination of postoperative urea nitrogen excretion has proved helpful in the assessment of individual nitrogen requirements.

Animal data indicate that the balanced nutrition of a brain dead liver donor, using moderate amounts of carbohydrate, lipid (long-chain fatty acids and possibly fish oil) and amino acids, is associated with improved function of the transplanted organ.[96] The value of donor or organ conditioning which aims to reduce ischaemia/reperfusion damage in man by provision of high doses of arginine or glutamine is unclear.

2.5. Water, electrolytes, vitamins, trace elements

Water, electrolytes, water- and fat-soluble vitamins and trace elements should be given daily in order to cover daily requirements (C).

Comments: body composition of cirrhotics is altered profoundly and characterised by protein depletion and accumulation of total body water even in Child-Pugh class A patients.[97,98] This goes hand-in-hand with salt retention, which therefore does not usually lead to hypernatraemia. On the contrary, depletion of potassium, magnesium, phosphate and other intracellular minerals are frequent. In an early study comparing PN vs. oral diet in cirrhotic patients with ascites, the response to diuretics was poorer in those patients receiving PN.[12]

No recommendation on the requirement of micronutrients can be made on the basis of controlled studies. As in other conditions, the administration of micronutrients has no proven therapeutic effect apart from the prevention or correction of deficiency states.

Supplementing zinc and vitamin A may indirectly improve food intake and nutritional state by improving dysgeusia.[99,100] Zinc and selenium deficiency have been observed in alcoholic and non-alcoholic liver disease.[101–104] An impressive association between HE and zinc deficiency has been described in case reports.[105,106] Controlled trials of oral zinc supplementation, however, have failed to prove a therapeutic effect on HE.[107–109] Urea production capacity increased after oral zinc application when previously subnormal plasma levels were normalised.[110]

A deficiency in water soluble vitamins, mainly group B vitamins, is common in cirrhosis, especially that of alcoholic origin.[111,112] Deficiency in fat-soluble vitamins has been observed in cholestasis-related steatorrhoea, bile salt deficiency, and in alcoholics.[113,114] Supplementation with calcium and vitamin D is recommended for patients with osteopenia, although this did not result in any improvement in bone density in patients with primary biliary cirrhosis; oestrogen substitution proved to be much more effective in female patients.[113,115]

In a pragmatic approach, liberal supplementation is recommended in the first two weeks of nutritional support, because the laboratory diagnosis of a specific trace element or vitamin deficiency may be more costly, and would delay provision. Due to the high prevalence of malnutrition in this patient group cirrhotic patients are in danger of developing refeeding syndrome and additional phosphate, potassium and magnesium may be required.

In transplanted patients the often pre-existing chronic dilutional hyponatraemia should be corrected carefully in order to avoid pontine myelinolysis.[116] Magnesium levels need to be monitored in order to detect and treat ciclosporin or tacrolimus induced hypomagnesaemia.[117] Postoperative hypophosphataemia and its possible relation to PN following right hemihepatectomy in living donors has been reported by some but not all study groups.[118–120]

3. Acute liver failure

Preliminary remarks: due to the substantial loss of liver cell function, acute liver failure (LF) is a serious condition characterised by profound metabolic dysfunction and is almost invariably complicated by multiple organ failure. Depending on the interval between the onset of jaundice and that of HE, hyperacute (interval < 8 days), acute (interval < 29 days) and subacute liver failure (interval 29–72 days) are distinguished.[121] There is a more favourable prognosis in hyperacute than in acute or subacute LF.

Despite the clinical significance of metabolic derangements like hypoglycaemia or hyperammonaemia and encephalopathy, there are only limited data from animal experiments or descriptive physiology data and no data from clinical trials, on which to base a rational metabolic intervention like nutritional therapy.

3.1. Indication and timing of PN

As in other critically ill patients artificial nutrition in acute LF is indicated when the patient is considered unlikely to resume normal oral nutrition within the next 5–7 days irrespective of current nutritional state. PN is helpful in patients who cannot be fed adequately by enteral nutrition.

Comments: in the treatment of acute LF, measures to stabilize the metabolism and vital functions and the treatment of brain oedema are of utmost importance. In this condition nutritional therapy has two objectives:

(1) ensuring the adequate provision of energy, especially assuring euglycaemia by giving glucose, lipid, vitamins and trace elements; and
(2) ensuring optimal rates of protein synthesis by providing an adequate intake of protein or amino acids, respectively.

3.2. Energy intake

In acute liver failure resting energy expenditure is increased 1.2- to 1.3-fold compared to healthy individuals. Whenever possible, the individual's energy requirement should be measured by use of indirect calorimetry (C).

Comments: surprisingly few liver units seem to measure or even calculate the energy expenditure of patients with acute liver failure[122] despite the well-known fact that hepatic energy

expenditure amounts to 25% of the overall energy expenditure.[123] A survey of 33 hepatology units in Europe showed that the resting energy expenditure was measured by only 12.5% of the centres by means of indirect calorimetry and that 53% usually used the Harris and Benedict formula. Energy requirements were not recorded in a third of centres.

In patients with acute LF, indirect calorimetry showed an increase in resting energy expenditure by 18% or 30%, respectively, in comparison with healthy controls.[124,125] In terms of energy expenditure, patients with acute LF are no different from critically ill patients with other aetiologies.

3.3. Nutrient intake

Sufficient glucose provision (2–3 g kg^{-1} d^{-1}) is mandatory for the prophylaxis and treatment of hypoglycaemia (C). Xylitol or sorbitol in exchange for glucose is of no proven benefit in acute LF; moreover, both have to be metabolised by the liver before they can be utilized.

In clinical practice glucose and lipid (0.8–1.2 g kg^{-1} d^{-1}) can be given simultaneously; the use of lipid may be especially advantageous in the presence of insulin resistance.

Amino acid administration is not mandatory in hyperacute LF. In acute or subacute LF, however, amino acids (0.8–1.2 g kg^{-1} d^{-1} in PN) or protein (0.8–1.2 g kg^{-1} d^{-1} in enteral nutrition) should be used in order to support protein synthesis.

Comments: hypoglycaemia is a clinically relevant and common problem in LF[126] resulting from a loss of hepatic gluconeogenetic capacity, lack of glycogen and hyperinsulinism.[127] As a standard procedure hypoglycaemia is treated by infusing glucose at a rate of 1.5–2 g kg^{-1} d^{-1}.[128,129] At the turn of the millennium the reported glucose infusion rates ranged from 6 to 10 g kg^{-1} d^{-1} and blood glucose levels below 10 mmol/l were aimed for by only 39% of participating centres.[122] Meanwhile, ensuring euglycaemia has been shown to confer a survival and morbidity benefit to critically ill patients regardless of aetiology.[70,71] Great care, however, must be taken to avoid hypoglycaemia.[72] Since cerebral oedema plays a crucial role in the prognosis of patients with acute liver failure, strict blood glucose control may be particularly advantageous. Ischaemia related damage of neurons and glial cells,[130] impaired leukocyte function[131] and oxidative stress have all been found to be associated with hyperglycaemia.

The oxidation of fatty acids and ketogenesis are the main energy yielding processes for hepatocytes.[132] Thus, adequate provision of lipid would be a plausible therapeutic objective provided there is sufficient oxygen supply to the hepatic tissue. It must be kept in mind, however, that some cases of acute LF, in particular those with microvesicular steatosis and mitochondrial dysfunction, are caused by an impairment of hepatic beta-oxidation. In such a case, exogenous lipid, even from administering propofol as a sedative, cannot be metabolised and may be harmful.[133,134] Unlike the situation in septic patients, the splanchnic viscera of LF patients do not take up but rather release free fatty acids.[135]

There are no systematic data on the role of lipid as a nutrient in this context. Exogenously applied lipid seems to be well tolerated by most patients.[136,137] According to the European survey two-thirds of participating hepatology centres gives parenteral lipid in patients with acute liver failure, the majority opting for an LCT/MCT emulsion.[122]

The plasma levels of amino acids are raised 3- to 4-fold in acute LF. The amino acid pattern is characterised by a decrease in branched chain amino acids and an increase in tryptophan, aromatic and sulfur-containing amino acids.[138–140] More recent data show that in LF the splanchnic organs do not take up amino acids in contrast to their net uptake in healthy humans and even in septic patients.[138]

The use of amino acid infusions has often been omitted for fear of aggravating existing hyperammonaemia and hyperaminoacidaemia and causing cerebral oedema and encephalopathy. In the survey, however, the majority reported giving i.v. amino acids.[122] Some clinicians reported use of standard amino acid solutions while the majority prescribed branched chain-enriched solutions aiming for a correction of the deranged plasma amino acid pattern.[85,141,142] Since elevated arterial ammonia levels have been recognized as an independent predictor of poor outcome in LF patients,[143–145] it seems prudent to adjust the provision of amino acids according to the ammonia levels monitored. While pathophysiological considerations provide a rationale for the use of liver-adapted solutions rich in branched-chain amino acids, no clinical trial in acute LF has shown an outcome benefit in comparison to standard solutions.

Adequate metabolic monitoring is necessary in order to adapt nutrient provision to substrate utilisation in order to prevent substrate overload due to inadequate intake. Strict control of the plasma levels of glucose (target: 5–8 mmol/L), lactate (target: <5.0 mmol/L), triglycerides (target: <3.0 mmol/L) and ammonia (target: <100 μmol/L) are necessary for this purpose.

Patients with hypophosphataemia after acetaminophen-induced liver damage have a better prognosis. Severe hypophosphataemia, however, results in respiratory insufficiency and dysfunction of the nervous system and erythrocytes,[146] and thus, serum phosphate levels should be monitored and corrected in order to support liver regeneration.

Conflict of interest

Conflict of interest on file at ESPEN (espenjournals@espen.org).

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