Hepatology – Guidelines on Parenteral Nutrition, Chapter 16

Hepatologie – Leitlinie Parenterale Ernährung, Kapitel 16

Abstract

Parenteral nutrition (PN) is indicated in alcoholic steatohepatitis (ASH) and in cirrhotic patients with moderate or severe malnutrition. PN should be started immediately when sufficientl oral or enteral feeding is not possible. ASH and cirrhosis patients who can be sufficiently fed either orally or enterally, but who have to abstain from food over a period of more than 12 hours (including nocturnal fasting) should receive basal glucose infusion (2–3 g/kg/d). Total PN is required if such fasting periods last longer than 72 h. PN in patients with higher-grade hepatic encephalopathy (HE); particularly in HE IV° with malfunction of swallowing and cough reflexes, and unprotected airways. Cirrhotic patients or patients after liver transplantation should receive early postoperative PN after surgery if they cannot be sufficiently rally or enterally nourished. No recommendation can be made on donor or organ conditioning by parenteral administration of glutamine and arginine, aiming at minimising ischemia/reperfusion damage. In acute liver failure artificial nutrition should be considered irrespective of the nutritional state and should be commenced when oral nutrition cannot be restarted within 5 to 7 days. Whenever feasible, enteral nutrition should be administered via a nasoduodenal feeding tube.

Keywords: non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, liver cirrhosis, hepatic encephalopathy, acute liver failure

Zusammenfassung

Bei Patienten mit Alkoholischer Steatohepatitis (ASH) oder Zirrhose mit mäßiger oder schwerer Mangelernährung, die auf oralem oder enteralem Wege nicht ausreichend ernährt werden können, ist der sofortige Beginn der PE (parenterale Ernährung) indiziert. ASH- oder Zirrhosepatienten, die auf oralem oder enteralem Wege ausreichend ernährt werden können, aber aus medizinischen Gründen eine vorübergehende, über 12 h hinausgehende Nahrungskarenz (nächtliche Nahrungskarenz mitrechnen) einhalten müssen, sollen eine basale Glukosezufuhr (2–3 $g \cdot kg^{-1} \cdot d^{-1}$) erhalten. Dauert diese Karenz länger als 72 h, ist eine totale PE indiziert. Bei höhergradiger hepatischer Enzephalopathie, insbesondere bei HE IV, ist bei gestörten Schutzreflexen und ungeschützten Atemwegen der parenterale Zufuhrweg für die Ernährung in Betracht zu ziehen. Des Weiteren sollten Zirrhosepatienten oder Patienten nach einer Lebertransplantation nach einem operativen Eingriff eine frühe postoperative (zusätzliche) PE erhalten, wenn sie auf oralem oder enteralem Wege nicht ausreichend ernährt werden können. Zur Frage der Spender- bzw. Organkonditionierung mit dem Ziel der Minimierung eines Ischämie-/Reperfusionsschadens durch parenterale Gabe von Glutamin und Arginin kann keine Empfehlung gegeben werden. Die Indikation zur künstlichen Ernährung bei akutem Leberversagen ist unabhängig vom Ernährungszustand dann zu sehen, wenn eine orale Ernährung innerhalb von 5–7 Tagen nicht wieder aufgenommen werden kann. Dabei ist in erster Linie die enterale Ernährung über eine nasoduodenale Sonde anzustreben.

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Schlüsselwörter: Fettleberhepatitis, alkoholische Lebererkrankung, Leberzirrhose, hepatische Enzephalopathie, akutes Leberversagen

Alcoholic steatohepatitis (ASH; alcoholic hepatitis + cirrhosis)

Indication and time of PN in ASH

- PN is indicated in ASH and should be immediately started in ASH patients with moderate or severe malnutrition, who *cannot* be sufficiently fed either orally or enterally (A).
- ASH patients who can be sufficiently fed either orally or enterally, but who have to abstain from food (including nocturnal fasting) for more then 12 hours should receive basal glucose infusion (2–3 g/kg/d) (C). Total PN is required if fasting periods last longer than 72 h (C).

Commentary

The nutritional state of the patient carries a prognostic significance in patients with ASH (III) [1], [2], [3]. Simple bedside methods like "subjective global assessment" or anthropometry are sufficient to identify at-risk patients, and are, therefore, recommended [4].
PN supplementation to ad lib oral nutrition was studied in seven controlled trials using conventional amino acid solutions. The parenteral intake provided approximately 200–3000 kcal/d, including 35–130 g amino acids per day, and the oral intake ranged from 13 to 39 kcal/kg/d [5], [6], [7], [8], [9], [10], [11], [12], [13]. No change in mortality was observed with this approach. This may be due to the inclusion of patients with low risk and only moderate disease severity. Adverse effects of increased nitrogen intake were not observed, although sensitive methods, able to detect minor degrees of hepatic encephalopathy, were not used. The majority of studies reported an improvement in visceral protein compartment (serum prealbumin, transferrin, total protein, total lymphocyte count), used as a measure of the nutritional state. An improvement in liver function (galactose elimination, serum bilirubin) was also described.
A late evening carbohydrate snack resulted in an improvement in protein metabolism in cirrhotic patients [14], [15], [16]. Therefore, it is recommended that in the event of a long fasting duration, patients should receive a basal glucose intake equal to the endogenous hepatic glucose production [14], [15], [16]. It is known that even an overnight fast in cirrhotic patients results in depletion of glycogen stores and metabolic conditions similar to that after prolonged starvation in normal individuals.

Energy intake

- In practice, an energy requirement equal to 1.3 times the basal metabolic rate, calculated by means of a formula, can be safely assumed for patients with ASH (C).

Commentary

According to an older study [17], ASH patients are not different from healthy persons with regards to the relationship between measured and predicted resting energy expenditure. ASH patients, however, show higher energy consumption when correlated to their reduced muscle mass (creatinine excretion in 24 h urine).
When hydration status is normal, the actual weight should be used as body weight for the calculation of the basal metabolic rate with the help of a formula [18]. In patients with ascites, the ideal weight according to the body height should be used for calculations.

Substrate intake with total PN

- Carbohydrates should be provided exclusively by glucose and cover 50–60% of non-protein energy requirements (C).
- Lipids should be provided using emulsions with a reduced content of polyunsaturated fatty acids compared to pure soybean oil emulsions and cover 40–50% of non-protein energy requirements (C).
- The amino acid intake should amount to 1.2 g/kg/d in patients who are either not malnourished or moderately malnourished, and 1.5 g/kg/d in severely malnourished patients (C).
- Water-soluble and fat-soluble vitamins as well as minerals and trace elements should be administered daily (cf. "Water, electrolytes, vitamins and trace elements" http://www.egms.de/en/gms/2009-7/000080.shtml) (C).

Commentary

These recommendations are based on those for PN in liver cirrhosis, which is already present in many cases of ASH. There are no systematic trials on the quantity and the formulation of PN for ASH.
Both water-soluble and fat-soluble vitamins should be administered daily in a standard TPN dosage. If necessary, administration of pharmacological doses of vitamin B1, as a therapy/prophylaxis for Wernicke's encephalopathy, or of vitamin K in cholestasis-related fat malabsorption or other vitamins may be additionally required to correct deficiencies. Trace elements should be administered daily in a standard total PN dose. A pragmatic recommendation is to routinely administer double the daily requirements of zinc (=2x10 mg/d).
This patient group is at great risk of developing refeeding syndrome (cf. "Complications and monitoring"

http://www.egms.de/en/gms/2009-7/000076.shtml) because of their tendency to be chronically malnourished.

Liver cirrhosis

Indication and time of PN in cirrhosis

- Immediate commencement of PN is indicated in cirrhotic patients with moderate or severe malnutrition, who cannot be sufficiently nourished either orally or enterally (C).
- Cirrhosis patients, who can be sufficiently nourished either orally or enterally, but who have to abstain temporarily from food (including nocturnal fasting) over a 12 hour period, should receive a basal glucose infusion (2–3 g/kg/d). Total PN is required if this fast lasts longer than 72 h (C).
- PN should be considered in patients with higher-grade hepatic encephalopathy (HE); particularly in HE IV° with malfunction of swallowing and cough reflexes, and unprotected airways (C).
- Cirrhosis patients should receive early postoperative (additional) PN after surgery, notwithstanding the recommendations for other patients, if they cannot be sufficiently nourished either orally or enterally (A).
- After liver transplantation, patients should receive early postoperative nutrition. PN is the option second to enteral nutrition (C).
- No recommendation can be made on the question of donor or organ conditioning, with the aim of minimising ischemia/reperfusion damage, by parenteral administration of glutamine and arginine (C).

Commentary

Numerous descriptive studies have shown higher rates of complications and mortality in cirrhotic patients with marked signs of protein malnutrition as well as a higher mortality rate when subjected to liver transplantation [19], [20], [21], [22], [23], [24], [25], [26].

Prevalence and severity of malnutrition are independent of the aetiology of liver disease [20], [27], [28], but correlate positively with the severity of the illness. The prevalence of PEM increases from 20% in stage A, by Child-Pugh criteria, to over 60% in stage C [27]. The daily food intake is of prognostic significance. Cirrhosis patients with a low, spontaneous energy intake showed the highest mortality in controlled studies investigating the efficiency of supplementary enteral nutrition [2], [29], [30], [31], [32]. There are no systematic trials on PN in cirrhotic patients without ASH.

Simple bedside methods like “Subjective Global Assessment” or anthropometry were able to sufficiently identify malnutrition, and the use of more complex score systems was not superior in this identification [4].

The recommendation of basal glucose intake to be equal to endogenous hepatic glucose production in the event of longer fasting is based on the findings that a late evening carbohydrate snack results in an improvement in protein metabolism of cirrhotic patients [14], [15], [16]. After an overnight fast, in cirrhotic patients, glycogen stores are depleted and metabolic conditions are similar to that after prolonged starvation in normal individuals.

Hepatic Encephalopathy (HE). In patients with hepatic encephalopathy, oral nutrition is often insufficient, even in low-grade encephalopathy (HE I°–II°) due to somnolence and psycho-motor dysfunction, such that enteral feeding is required to provide adequate nutrition. PN should be considered in patients with higher-grade encephalopathy (HE), particularly in HE IV°, when there is malfunctioning of swallowing and cough reflexes in the presence of unprotected airways. In clinical practice, enteral nutrition in patients with acute liver failure [33] and the results of the study by Keohane et al. on malnourished patients with liver cirrhosis and acute encephalopathy [34] demonstrate the feasibility of enteral nutrition in comatose cirrhotic patients. There are no published systematic comparisons between enteral and parenteral nutrition in patients with liver cirrhosis and encephalopathy.

In malnourished cirrhotic patients, the risk of post-operative complications, including mortality, is increased after abdominal operations [35].

After visceral surgery, cirrhotic patients have a lower rate of complications when postoperative nutritional therapy is given instead of just fluid and electrolytes [36], [37] (Ib).

Surgery and Transplantation. Postoperative nutrition of transplant patients confers the advantage of shorter time on mechanical ventilation and shorter stay in the intensive care unit compared to just fluid and electrolyte infusions [38] (Ib). In a direct comparison between parenteral and early enteral nutrition, both strategies were equally efficient with regards to the maintenance of nutritional state [39]. However, lower incidence of viral infections, and improved nitrogen retention were observed in patients who had been given early enteral nutrition, 12 hours after the transplantation [40].

At present, the value of donor or organ conditioning, by means of high doses of arginine intake, with the aim of minimising ischemia/reperfusion damage is uncertain.

Energy intake

- The energy requirement of many patients with liver cirrhosis amounts to 1.3 times the basal metabolic rate, calculated by means of a formula (B).

Commentary

Measured resting energy expenditure is higher than predicted by the Harris Benedict formula in up to 30–35% of cirrhotic patients (hypermetabolism), and below the predicted value in 18% of the patients [41], [42]. Cirrhotic patients can also have a hypermetabolic state [43], defined as measured basal metabolic rate versus value

calculated from measured body cell mass by regression analysis.

In order to classify patients according to metabolic rate, indirect calorimetry is required. Therefore, up to now these findings remain without consequence in clinical practice. Furthermore, the few publications on total energy expenditure in patients with liver cirrhosis indicate that the 24h energy requirement of cirrhotic patients is 130% of the basal metabolic rate [44], [45]. Diet-induced thermogenesis [46], [47], [48] and energy requirements for physical activity in stable cirrhosis patients [49], [50], [51] also show no deviation from those in healthy patients. Obviously, an increased energy requirement in advanced illness is compensated for by diminished physical activity reflecting poor physical condition [32], [51].

When hydration status is normal, the actual weight should be used as body weight for the calculation of the basal metabolic rate according to a formula [18]. In patients with ascites, the ideal weight according to body height should be used for calculations.

Patients with liver transplantations have average energy requirements similar to the majority of patients with major abdominal surgery. In these patients too, an intake of non-protein energy of 1.3-fold the basal metabolic rate is generally sufficient [52], [53]. In a longitudinal study, postoperative hypermetabolism peaked 10 days after the transplantation at 124% of the predicted basal metabolic rate [54]. There was no difference between measured and predicted basal metabolic rate at 6–12 months post transplantation [54], [55]. Hyperalimentation should be avoided.

Substrate intake – general

- If PN is used as the exclusive form of nutrition, all necessary macro- and micro-nutrients must be administered with PN (C).
- Carbohydrate intake should exclusively be provided by glucose and cover 50–60% of non-protein energy requirements (cf. "Carbohydrates" http://www.egms.de/en/gms/2009-7/000082.shtml) (C).
- Lipid should be provided by using emulsions with a reduced content of polyunsaturated fatty acids, as compared to pure soy bean oil emulsions, and cover 40–50% of non-protein energy requirements (C).
- PN-related hyperglycaemia should be consequently avoided (A).
- A reduction in carbohydrate intake to 2–3 g/kg/d and continuous insulin administration, if needed, should be carried out in case of hyperglycaemia (C).

Commentary

Insulin resistance in liver cirrhosis. In the fasting state, substrate utilisation is characterised by an increased rate of lipid oxidation and frequent occurrence of insulin resistance, even in Child-Pugh stage A of the illness [41], [56], [57], [58]. Insulin resistance induces reduced glucose uptake and dysfunctional non-oxidative glucose utilisation with reduced glycogen synthesis in skeletal muscles during fasting, while glucose oxidation and lactate production return to normal after glucose administration [47], [59], [60]. Some 15–37% of cirrhotic patients develop overt diabetes indicating an unfavourable prognosis [61], [62].

There is growing evidence of a treatment advantage in various clinical conditions when euglycaemia is maintained. It seems justified to also recommend this strategy for patients with liver cirrhosis who are receiving PN (cf. "Carbohydrates" http://www.egms.de/en/gms/2009-7/000082.shtml and "Intensive medicine" http://www.egms.de/en/gms/2009-7/000073.shtml).

In the early postoperative phase, a dysfunction of glucose metabolism associated with insulin resistance is often prevalent. In this situation, hyperglycaemia should be treated by reducing the glucose intake, because higher insulin doses do not improve glucose oxidation [63].

When tacrolimus is used for immunosuppression, its diabetogenic potential can be lowered by reducing the dose and aiming for trough levels of 3–8 ng/ml without undue risk of rejection [64].

Lipid tolerance and MCT/LCT. Only few data are available on the ideal composition of the main energy-supplying substrates, carbohydrates and lipids. Plasma clearance and oxidation of infused lipids is normal in cirrhotic patients [65], [66]. Glucose and lipids have been used as energy-supplying substrates in a caloric ratio of 40–50:50–60 (G:L) in two trials [67], [68]. There are findings suggesting more favourable substrate and metabolite concentrations when infusing both glucose and lipid compared to glucose as the sole energy substrate [69]. Improved functioning of the reticulo-endothelial system was observed (cf. "Surgery and transplantation" http://www.egms.de/en/gms/2009-7/000069.shtml) when using MCT/LCT emulsions (with a lower content of polyunsaturated fatty acids as compared to pure soy bean oil emulsions) after liver transplantation.

Substrate intake – amino acids

- Amino acids should be administered in a dose of 1.2 g/kg/d in compensated cirrhosis without severe malnutrition, and in a dose of 1.5 g/kg/d in decompensated cirrhosis with severe malnutrition (A).
- A standard solution should be given in encephalopathy ≤ grade II and a liver-adapted complete solution should be given in encephalopathy grades III–IV. These solutions contain an increased amount of branched-chain amino acids (BCAA) and lower content of aromatic amino acids, methionine and tryptophan (A).

Commentary

Compensated cirrhosis. For PN, these patients do not require an amino acid solution with a special "hepatic formula" composition. In clinical studies, the protein or amino acid intake in patients with liver cirrhosis and severe encephalopathy was between 0.6 and 1.2 g/kg/d

Table 1: Parenteral amino acid solutions with an increased content of branched-chain amino acids available in Germany

	Aminofusin® 5% Hepar	Aminoplasmal® Hepa 10%	Aminosteril® n-Hepa 8%	Hepar 10% Pfrimmer	PARENTAMIN® Hepa 10%	salviamin® hepar
Electrolyte-free	no	yes	yes	yes	no	yes
Carbohydrate (Xylitol)[g/l]	–	–	–	–	–	–
Total AA[g/l]	50	100	80	100	100	60
BCAA/total AA[%]	45	33	42	35	33	35.6
Aromatic AA + Trp + Met/ total AA[%]	1.7	5	3.4	3.2	5	2.3
Isoleucine [g/l]	**7.6**	**8.8**	**10.4**	**11.1**	**8.8**	**6.78**
Leucine [g/l]	**8.5**	**13.6**	**13.09**	**13.5**	**13.6**	**8.28**
Valine [g/l]	**6.4**	**10.6**	**10.08**	**10.4**	**10.6**	**6.3**
Methionine [g/l]	0.5	1.2	1.1	1.2	1.2	0.45
Phenylalanine [g/l]	0.25	1.6	0.88	1.2	1.6	0.6
Tryptophan [g/l]	0.1	1.5	0.7	0.8	1.5	0.38
Tyrosine [g/l]	–	0.7	–	–	0.7	–
Arginine [g/l]	4.9	8.8	10.72	9.6	8.8	4.5
Alanine [g/l]	2.1	8.3	4.64	9.2	8.3	5.48
Glutamic acid [g/l]	1.0	5.7	–	–	5.7	–
Glycine [g/l]	0.7	6.3	5.82	11.0	6.3	6.75
Histidine [g/l]	0.6	4.7	2.8	3.0	4.7	1.88
Lysine [g/l]	4.1	7.51	6.88	7.5	7.51	5.55
L-Asparagine [g/l]	–	0.48	–	–	0.48	–
Aspartic acid [g/l]	4.03	2.5	–	–	2.5	–
Ornithine [g/l]	4.0	1.3	–	–	1.3	–
Proline [g/l]	1.2	7.1	5.73	9.8	7.1	6.0
Serine [g/l]	2.75	3.7	2.24	6.1	3.7	3.45
Threonine [g/l]	1.2	4.6	4.4	5.6	4.6	3.38
Cystein [g/l]	0.15	0.59	0.52	–	0.59	0.25

AA: amino acids; BCAA: branched-chain amino acids

[70]. In patients with alcoholic hepatitis or cirrhosis with or without low-grade encephalopathy, the intake was between 0.5 and 1.6 g/kg/d [5], [6], [7], [9], [10], [11], [12], [13], [29], [30] [31], [71]. An explicit and systematic determination of the protein requirement has, however, been carried out only in a few studies. In these studies, patients with stable cirrhosis were found to have an increased protein requirement of 1.2 g/kg/d in contrast to the value of 0.8 g/kg/d in healthy humans [32], [44], [72], [73].

Cirrhosis with encephalopathy. Liver-adapted amino acid solutions containing increased proportions of branched-chain (35–45%) and a reduced proportion of aromatic amino acids as well as a reduced proportion of methionine and tryptophan have been introduced for patients with liver diseases [74], [75], [76] (Table 1). These solutions help to correct the amino acid imbalance existing in liver cirrhosis. “Coma solutions” are available in some countries, which contain either exclusively BCAAs, or other additional substances supposed to be effective in hepatic encephalopathy. The solutions are incomplete, and, therefore, should only be used to target the pharmacological correction of an amino acid imbalance and not as the exclusive nitrogen source for PN.

The effectiveness of branched-chain amino acids in the treatment of hepatic encephalopathy has been tested in seven controlled studies [77], [78], [79], [80], [81]; the results of which are, however, contradictory. It is extremely difficult to detect a treatment effect on hepatic encephalopathy, when at the same time complications of cirrhosis are present like gastrointestinal bleeding, sepsis or renal failure, which dominate the clinical results. A meta-analysis of these studies shows a beneficial effect of the BCAA-enriched solutions with regards to mental state, but not with regards to survival [70]. In a Cochrane analysis, a subgroup of the seven randomised controlled

studies was analysed, with a total of 397 patients with acute hepatic encephalopathy, who were treated with intravenously administered BCAAs in the intervention group [82]. The parenteral BCAA administration had a significant positive effect on the improvement of hepatic encephalopathy; the period of survival, however, remained unchanged.

Surgery and transplantation. After liver resection, oesophagus transection with splenectomy or splenorenal shunt in patients with liver cirrhosis, no increased encephalopathy rate was observed when a conventional amino acid solution (50 g/24 h) was used for postoperative nutrition instead of a BCAA-enriched amino acid solution (40 g/24 h) [37]. No difference was observed between a standard or a BCAA-enriched amino acid solution after liver transplantation either [38].

Transplanted patients exhibit a noteworthy nitrogen loss with a continuously negative nitrogen balance up to 28 days post surgery [52], [83], therefore protein or amino acid intake should be increased appropriately. A protein or amino acid intake of 1.0–1.5 g/kg-/d was mostly used in studies [24], [38]. The determination of postoperative urea-nitrogen excretion was helpful in ascertaining individual nitrogen requirements.

Conditioning of organ donors. Data mainly derived from experimental studies indicate that the balanced nutrition of a "brain-dead" liver donor with moderate amounts of carbohydrates, lipids (long-chain fatty acids and possibly fish oil) and amino acids is associated with an improved function of the transplanted organ [84]. The value of donor or organ preconditioning against ischemia/reperfusion damage e.g. by means of high doses of arginine is at present uncertain.

Water, electrolytes, vitamins, trace elements

- Water, electrolytes, water- and fat-soluble vitamins as well as trace elements should be administered daily (cf. "Water, electrolytes, vitamins and trace elements" http://www.egms.de/en/gms/2009-7/000080.shtml) (C).

Commentary

Patients with liver cirrhosis have profound alterations in body composition with an increase in total body water already in Child-Pugh stage A [85]. This goes along with salt retention, which does not manifest in hypernatraemia. In contrast, potassium, magnesium, phosphate and other intracellular minerals are frequently depleted.

No recommendations on the requirements of micronutrients can be made on the basis of controlled studies. The administration of micronutrients has no effect on the nutritional state other than in the adjustment of a deficiency.

Supplementations of zinc and vitamin A might indirectly improve the food intake and nutritional state by improving dysgeusia [86], [87]. Zinc and selenium deficiencies were observed in alcoholic and non-alcoholic liver disease [88], [89], [90], [91]. A striking association between hepatic encephalopathy and zinc deficiency has been described in case reports [92], [93]. Oral zinc supplementation, however, has shown no effectiveness in subclinical encephalopathy in controlled studies [94], [95], [96]. Urea production capacity increased after oral zinc supply when the previously lowered plasma levels were normalised [97].

A deficiency in water-soluble vitamins is common in cirrhosis, especially of alcoholic origin [98], [99]. Deficits in fat-soluble vitamins are observed in cholestasis-related steatorrhoea, bile salt deficiency and in alcoholics [100], [101]. 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, with oestrogen substitution proving to be much more effective in female patients [100], [102].

In practice, liberal supplementation is recommended in the first two weeks of treatment as the laboratory diagnosis of a specific trace element or vitamin deficiency may be more expensive. Due to high prevalence of malnutrition in this group of patients, they are in danger of developing re-feeding syndrome (cf. "Complications and monitoring" http://www.egms.de/en/gms/2009-7/000076.shtml).

After transplantation, the often chronic hyponatraemia should be corrected carefully in order to avoid the risk of pontine myelinosis [103]. It is recommended to regularly check magnesium levels in order to determine cyclosporine- or tacrolimus-induced hypomagnesaemia [104].

Some, but not all study groups, reported the risk of postoperative hypophosphataemia and its possible connection with PN following right hemihepatectomy in a living donor [105], [106], [107].

Acute liver failure

Due to the massive loss of liver cell function, acute liver failure is a serious condition characterised by profound metabolic dysfunctions and almost invariably complicated by multi-organ failure. Depending on the interval till the onset of hepatic encephalopathy (HE), hyperacute (onset of jaundice till HE <8 days), acute (interval <29 days) and sub-acute liver failure (interval 29–72 days) are distinguished [108]. Prognosis is more favourable in hyperacute LF (liver failure) than in acute or subacute LF.

Despite the clinical significance of metabolic derangements like hypoglycaemia or hyperammonaemia and encephalopathy, there is only scarce animal-experiment or physiologically descriptive data, and no published clinical studies, on which a metabolic intervention like nutritional therapy could be based.

Indication and time of PN

- In analogy to intensive care patients, in acute LF artificial nutrition should be considered irrespective of the nutritional state and should be commenced when oral nutrition cannot be restarted within 5 to 7 days (cf. "Intensive medicine" http://www.egms.de/en/gms/2009-7/000073.shtml)
- Whenever possible, enteral nutrition should be administered via a nasoduodenal feeding tube (C).

Commentary

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

1. ensuring the adequate provision of required energy, especially euglycaemia, by giving glucose, lipids, vitamins and trace elements, and
2. ensuring optimal rates of protein synthesis by providing an adequate intake of protein or amino acids.

Energy intake

- In acute liver failure a hypermetabolic state can occur. The individual energy requirement should preferably, be determined measuring energy expenditure with indirect calorimetry, or be estimated with a formula (C).

Commentary

Surprisingly few liver units seem to measure, or at least calculate, the energy expenditure of patients with acute liver failure [33] despite the well-known fact that hepatic energy expenditure amounts to 25% of the overall energy expenditure [109]. A survey of 33 hepatology units in Europe showed that the resting energy expenditure was measured by 12.5% of the centres by means of indirect calorimetry, and that 53% usually used the Harris-Benedict formula; the energy requirements were not recorded in a third of centres.
In patients with acute liver failure, indirect calorimetry showed an increase in resting energy expenditure, in two studies, by 18 or 30% in comparison with healthy controls [110], [111]. Obviously, patients with acute liver failure are different from other critically ill patients regarding energy expenditure (cf. "Intensive medicine" http://www.egms.de/en/gms/2009-7/000073.shtml).

Substrate intake

- Sufficient glucose administration (2–3 g/kg/d) is mandatory for prophylaxis or treatment of hypoglycaemia (C). Glucose substitutes are of no proven benefit in acute LF. Moreover, xylitol, sorbitol and fructose have to be metabolised by the liver before they can be utilized.
- Simultaneous infusion of glucose and lipid (0.8–1.2 g/kg/d) and offers benefits regarding insulin resistance and should be used.
- Amino acid administration is not necessary in hyperacute LF. Amino acids (0.8–1.2 g/kg/d in PN) or protein (0.8–1.2 g/kg/d in enteral nutrition) should be used in acute or sub-acute LF in order to support protein synthesis.

Commentary

Glucose

In LF clinically significant hypoglycaemia [112] occure and results from a loss of hepatic gluconeogenetic capacity, lack of glycogen and hyperinsulinism [113]. It is widely accepted to treat hypoglycaemia by infusing 1.5–2 g glucose/kg body weight [114], [115]. At the end of the 1990's, the administration of glucose doses of 6 to 10 g per kg body weight per day was practised: a blood glucose level of under 10 mmol/l was aimed for by only 39% of centres [33]. Meanwhile, the landmark study by v. d. Berghe showing that euglycaemic metabolic control improved survival has likely been helpful in setting the standard also in acute liver failure [116].
As the progress of brain oedema mainly determines the prognosis of these patients, for pathophysiological reasons, strict blood glucose control may be particularly advantageous. Increased ischemia-related damage of neurons and glia cells [117], dysfunctional leukocyte function [118] or oxidative stress have been found to be associated with hyperglycaemia. The aministration of up to 4 IU/h insulin is recommended in order to adjust blood glucose levels and maintain euglycaemia (cf. "Carbohydrates" http://www.egms.de/en/gms/2009-7/000082.shtml and "Intensive medicine" http://www.egms.de/en/gms/2009-7/000073.shtml).

Lipids

The oxidation of fatty acids and ketogenesis are the main energy-providing processes for hepatocytes [119]. Thus, adequate lipid administration would be a plausible, therapeutic objective provided there is sufficient oxygen supply to the liver tissues. Some cases of acute liver failure are, however, caused by an impairment of hepatic beta-oxidation. In these specific cases, exogenous lipid, e.g. even administering Propofol as a sedative, cannot be metabolised and can become potentially harmful [120], [121]. Measurements of substrate turnover in a study showed that there was no fatty acid absorption, but a release of free fatty acids from the splanchnic area in patients with acute liver failure in comparison to septic patients [122].
There is no systematic data on the role of lipids as a nutrient. Exogenously administered lipids seem to be well tolerated by most patients [123], [124]. A survey of hep-

atology centres also showed that two-thirds of the centres administer parenteral lipids in patients with acute liver failure, mainly in the form of LCT/MCT emulsions [33].
Special attention should, however, be paid when giving lipids to patients with acute liver failure and microvesicular steatosis, in whom mitochondrial dysfunction is predominant.
Monitoring should be carried out as described in the chapter on "Complications and monitoring" http://www.egms.de/en/gms/2009-7/000076.shtml.

Amino acids

The plasma levels of amino acids are raised 3 to 4 fold in acute liver failure. The amino acid pattern is altered, and shows a relative decrease in branched-chain amino acids and a relative increase in tryptophan, aromatic and sulphurous amino acids [125], [126], [127]. More recent data shows that the splanchnic organs cannot take up amino acids in the event of liver failure while a net uptake of amino acids can be seen in healthy humans and even in septic patients [127].
Amino acid infusion was not used as often in the past for fear of aggravating existing hyperammonaemia and hyperaminoacidaemia, and causing brain oedema and encephalopathy. In the survey of hepatology centres, more than half of the centres indicated, however, that amino acids are infused [33]. A few centres use standard amino acid solutions, while the majority use incomplete solutions with branched-chain amino acids or complete solutions enriched with branched-chain amino acids in order to correct the altered amino acid pattern and optimise the nitrogen supply [74], [128], [129].
While pathophysiological considerations provide a rationale for the use of liver-adapted solutions with an increased proportion of branched-chain amino acids, no advantage could, however, be proven in comparison to standard solutions.
An adequate metabolic monitoring is necessary in order to ensure substrate supply, which is adjusted for substrate utilisation, and to prevent substrate overload. Strict control of the plasma glucose levels (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 [130], and thus, serum phosphate levels should be controlled stringently and corrected in order to support liver regeneration.

Notes

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