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ESPEN GUIDELINES

ESPEN Guidelines on Enteral Nutrition: Liver disease ☆

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Summary Enteral nutrition (EN) by means of oral nutritional supplements (ONS) and tube feeding (TF) offers the possibility to increase or to insure nutrient intake in case of insufficient oral food intake.

The present guideline is intended to give evidence-based recommendations for the use of ONS and TF in patients with liver disease (LD). It 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 discussed and accepted in a consensus conference.

EN by means of ONS is recommended for patients with chronic LD in whom undernutrition is very common. ONS improve nutritional status and survival in severely malnourished patients with alcoholic hepatitis. In patients with cirrhosis, TF improves nutritional status and liver function, reduces the rate of complications and prolongs survival. TF commenced early after liver transplantation can reduce

Abbreviations: Normal food, Normal diet of an individual as offered by the catering system of a hospital including special diets e.g. gluten-free, lactose free etc. diets; ASH, Alcoholic steatohepatitis; BCAA, Branched chain amino acids; BIA, Bioelectric impedance analysis; EN, Enteral nutrition. This is used as a general term to include both ONS and tube feeding. When either of these modalities is being discussed separately this is specified in the text; LC, liver cirrhosis; NASH, Non-alcoholic steatohepatitis; ONS, Oral nutritional supplements; SGA, Subjective global assessment; TF, Tube feeding

☆For further information on methodology see Schütz et al.[55] For further information on definition of terms see Lochs et al.[56]

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Undernutrition; BCAA

complication rate and cost and is preferable to parenteral nutrition. In acute liver failure TF is feasable and used in the majority of patients.

The full version of this article is available at www.espen.org.

Summary of statements: Alcoholic steatohepatitis

Subject	Recommendations	Grade[55]	Number
General	Use simple bedside methods such as the Subjective Global Assessment (SGA) or anthropometry to identify patients at risk of undernutrition.	C	1.1
	Recommended energy intake: 35–40 kcal/kg BW/d (147–168 kJ/BW Kg/d)	C	1.3
	Recommended protein intake: 1.2–1.5 g/kgBW/d	C	1.3
Application	Use supplementary enteral nutrition when patients cannot meet their caloric requirements through normal food.	A	1.2
	In general, oral nutritional supplements are recommended.	B	1.3
Route	Use tube feeding if patients are not able to maintain adequate oral intake (even when oesophageal varices are present)	A	1.3
	PEG placement is associated with a higher risk of complications and is not recommended.	C	1.3
Type of formula	Whole protein formulae are generally recommended.	C	1.3
	Consider using more concentrated high-energy formulae in patients with ascites.	C	1.3
	Use BCAA-enriched formulae in patients with hepatic encephalopathy arising during enteral nutrition.	A	1.3

Grade: Grade of recommendation; Number: refers to statement number within the text.

Summary of statements: Liver cirrhosis (LC)

Subject	Recommendations	Grade[55]	Number
General	Use simple bedside methods such as the Subjective Global Assessment (SGA) or anthropometry to identify patients at risk of undernutrition.	C	2.1
	Use phase angle or body cell mass measured by bioelectric impedance analysis (BIA) to quantitate undernutrition, despite some limitations in patients with ascites.	B	2.1
	Recommended energy intake: 35–40 kcal/kgBW/d (147–168 kJ/kgBW/d)	C	2.3
	Recommended protein intake: 1.2–1.5 g/kgBW/d	C	2.3
Application	Use supplemental enteral nutrition when patients cannot meet their caloric requirements through oral	A	2.2

	food despite adequate individualised nutritional advise.		
Route	If patients are not able to maintain adequate oral intake from normal food, use		
	• Oral nutritional supplements or	C	2.3
	• Tube feeding (even in the presence of oesophageal varices)	A	2.3
	PEG placement is associated with a higher risk of complications and is not recommended.	C	2.3
Type of formula	Whole protein formulae are generally recommended.	C	2.3
	Consider using more concentrated high-energy formulae in patients with ascites.	C	2.3
	Use BCAA-enriched formulae in patients with hepatic encephalopathy arising during enteral nutrition.	A	2.3
	The use of oral BCAA supplementation can improve clinical outcome in advanced cirrhosis.	B	2.3
Outcome	Enteral nutrition improves nutritional status and liver function, reduces complications and prolongs survival in cirrhotics and is therefore recommended.	A	2.4

Grade: Grade of recommendation; Number: refers to statement number within the text.

Summary of statements: Transplantation and surgery

Subject	Recommendations	Grade[55]	Number
General	Use simple bedside methods such as the Subjective Global Assessment (SGA) or anthropometry to identify patients at risk of undernutrition.	C	3.1
	Use phase angle or body cell mass measured by bioelectric impedance analysis to quantitate undernutrition, despite some limitations in patients with ascites.	B	3.1
Indication			
Preoperative	Follow recommendations for cirrhosis.		3.2
Postoperative	Initiate normal food/enteral nutrition within 12–24 h postoperatively.	B	3.2
	Initiate early normal food or enteral nutrition after other surgical procedures.	B	3.2
Application			
Preoperative	Follow recommendations for cirrhosis.		
	For children awaiting transplantation consider BCAA administration.	B	3.3
Postoperative	Recommended energy intake: 35–40 kcal/kgBW/d (147–168 kJ/kgBW/d)	C	3.3
	Recommended protein intake: 1.2–1.5 g/kgBW/d	C	3.3
Route			
Preoperative	Follow recommendations for cirrhosis.		
Postoperative	Use nasogastric tubes or catheter jejunostomy for early enteral nutrition.	B	3.3

Type of formula			
Preoperative	Follow recommendations for cirrhosis.		3.3
Postoperative	Whole protein formulae are generally recommended.	C	3.3
	In patients with ascites prefer concentrated high-energy formulae for reasons of fluid balance.	C	3.3
	Use BCAA-enriched formulae in patients with hepatic encephalopathy arising during enteral nutrition.	A	3.3
Outcome			
Preoperative	An improvement of perioperative mortality or complication rate by preoperative tube feeding or oral nutritional supplements has not yet been shown.		
	However, a clear recommendation for nutritional therapy in undernourished patients with liver cirrhosis is supported by the statements concerning nutrition in LC made in statement 2.4.	C	3.4
Postoperative	Early normal food or enteral nutrition is recommended for transplant and surgery patients with LC in order to minimise perioperative—in particular infectious—complications.	B	3.4

Grade: Grade of recommendation; Number: refers to statement number within the text.

1. Alcoholic steatohepatitis (ASH)

Preliminary remarks: There are no randomised controlled trials available on nutritional therapy in non-alcoholic steatohepatitis (NASH). Unlike alcoholic steatohepatitis (ASH), NASH often is associated with overnutrition and insulin resistance. Therefore recommendations given for ASH cannot easily be applied to NASH despite remarkable similarities. Nutritional recommendations for NASH patients focus on the underlying disease (metabolic syndrome, other secondary causes).

1.1. Does nutritional status influence outcome in ASH? Which is the best widely applicable method to assess nutritional status?

The prognostic value of nutritional status in patients with alcoholic hepatitis has been demonstrated (III). Simple bedside methods such as the Subjective Global Assessment (SGA) or anthropometry are considered adequate for identifying patients at risk (C).

Comment: Several publications from the American Veteran Affairs (VA) study report a higher rate of complications and mortality in undernourished ASH patients.[1–3] In order to identify undernutrition, a scoring system consisting of variables such as actual/ideal weight, anthropometry, creatinine index, visceral proteins, absolute lymphocyte count, delayed type skin reaction was used in these studies. This composite scoring system includes unreliable variables such as plasma concentrations of visceral proteins or 24-h urine creatinine excretion and has been modified repeatedly, the most recent publication of the series also reported a prognostic significance of the variables absolute CD8+count and hand grip strength.[3] Moreover, a clear association between low intake of normal food and high mortality was found.[2]

1.2. When is EN indicated or contraindicated?

Supplementary enteral nutrition (EN) is indicated when ASH patients cannot meet their caloric requirements through normal food (A) and when there are no contraindications like ileus (C).

Comment: These recommendations are based on six trials studying EN in 465 ASH patients,[1–6] of which only three trials were randomised[4–6] (Ib).

The American VA studies compared the effects of anabolic steroids vs. placebo together with the effects of high energy and protein oral nutritional supplements (ONS) enriched with branched chain-amino acids (BCAA) vs. low energy and protein ONS.[2,3] The publications from 1993/1995 contain a joint and summarizing evaluation of the VA studies #275 and #119 that had already been published

separately,[1] and the results of these publications are therefore difficult to interpret.[1–3] They show, however, that a higher energy and protein intake can be achieved either by ONS or tube feeding (TF) even in severely undernourished ASH patients. Although EN appears to be preferable to parenteral nutrition, there has been no large randomised trial comparing the two methods in ASH patients.

In summary, the results of these studies show, that supplementary EN ensures adequate energy and protein intake without the risk of complications such as hepatic encephalopathy (Ib).

1.3. How should EN be delivered?

- *Which formula?*
- *Which method of delivery?*
- *What dosage?*

Whole protein formulae are generally recommended (C). More concentrated high-energy formulae are preferable in patients with ascites to avoid positive fluid balance (C).

BCAA-enriched formulae should be used in patients with hepatic encephalopathy arising during EN (A).

In general, ONS are recommended (B). If patients are not able to maintain adequate oral intake, TF is recommended (even when oesophageal varices are present) (A).

Placement of PEG is associated with a higher risk of complications (due to ascites or varices) and is not recommended (C).

An energy intake of 35–40 kcal/kgBW/d (147–168 kJ/kgBW/d) and a protein intake of 1.2–1.5 g/kgBW/d are recommended (C).

Comment: BCAA-enriched formulae were used in the American VA studies,[1–3] whereas other studies used casein[5] or intact protein with additional BCAA as a nitrogen source.[6]

A direct comparison between standard formula and BCAA enriched formula has not yet been made so that general recommendations cannot be made concerning the value of BCAA-enriched formulae in ASH patients.

Recommendations regarding the amount of nutrients are derived from those[1–3,5,6] given in published studies (Ib).

There is no evidence in the current literature[6–9] (Ib) that oesophageal varices pose any risk to the use of fine bore nasogastric tubes for TF.

1.4. Does EN improve nutritional status, liver function, and prognosis?

EN ensures adequate energy and protein intake without the risk of complications such as hepatic encephalopathy (Ib).

EN was as effective as steroids in patients with severe alcoholic hepatitis. However, survivors who had been treated with EN showed a lower mortality rate in the following year.

Comment: The influence of EN on the clinical course of liver disease (LD) cannot be judged satisfactorily from the available data. In a randomised placebo-controlled trial no difference in 28-day-mortality was found between the groups receiving EN and those receiving steroids. In the latter however, the mortality rate due to infectious complications in the following year was higher[6] (Ib). A possible synergistic effect of the two treatments should be investigated.

In a pooled evaluation of the two American VA studies (only one randomised) a significant reduction in mortality was found in the subgroup of those severely undernourished patients who achieved an adequate intake of BCAA-enriched ONS.[2] The subgroup of patients with moderate undernutrition, receiving the steroid oxandrolone and nutritional therapy, had a better outcome than the group receiving oxandrolone alone.[2] These findings suggest that adequate nutritional intake is a prerequisite for a positive treatment effect of oxandrolone.

So far, there is no evidence that EN has any impact on liver function in ASH[2,6] (IIa).

Further evaluation of the VA database showed that, in ASH patients whose encephalopathy can be managed with standard treatment such as lactulose, a low protein intake was associated with a worsening of encephalopathy whereas a normal protein intake (1 g/kgBw/d) was associated with an amelioration[8,10] (Ib).

2. Liver cirrhosis (LC)

2.1. Does nutritional status influence outcome in patients with LC? What is the best widely applicable method to assess nutritional status?

Undernutrition adversely affects the prognosis in patients with LC (III).

Simple bedside methods such as the SGA or anthropometry are considered adequate to identify patients at risk (C).

In order to quantitate undernutrition the determination of phase angle α or body cell mass (BCM) using bioelectrical impedance analysis (BIA) is recommended, despite some limitations in patients with ascites (B).

Comment: Several descriptive studies report higher rates of complications and mortality for LC patients with severe undernutrition, as well as higher mortality following liver transplantation.[11–20]

For the identification of undernutrition bedside methods, such as the SGA or anthropometry or measurement of handgrip strength[21] are considered adequate; the use of composite scores did not provide any additional value.[22]

Accurate quantitative measurement of nutritional status is difficult in the presence of fluid overload or impaired hepatic protein synthesis (e.g. albumin)[23] and necessitates sophisticated methods such as total body potassium count, dual energy X-ray absorptiometry (DEXA), in vivo neutron activation analysis (IVNAA) and isotope dilution.[22] Among bedside methods of measuring nutritional status in patients with cirrhosis, the determination of phase angle α or BCM using BIA is considered superior to methods such as anthropometry and 24 h creatinine excretion,[24–26] despite some limitations in patients with ascites.[27,28]

2.2. When is EN indicated or contraindicated?

Supplemental EN is indicated when LC patients cannot meet their nutritional requirements from normal food despite adequate individualised nutritional counselling (A).

Comment: LC patients should achieve an energy intake of 35–40 kcal/kgBW/d (147–168 kJ/kgBW/d) and a protein intake of 1.2–1.5 g/kgBW/d.[18] If oral intake is not adequate despite nutritional counselling, then additional ONS or TF should be commenced. In severely undernourished patients with advanced LC supplemental EN, in addition to normal food ad libitum, is of documented value[7,8] (Ib). In patients with less advanced LC additional ONS yielded no better results than normal food combined with nutritional counselling[29] (Ib). When deciding the most suitable method of feeding patients with advanced encephalopathy, the risk of aspiration during TF must be weighed against the potential complications of parenteral nutrition.

2.3. How should EN be delivered?

- ***Which formula?***
- ***Which method of delivery?***
- ***What dosage?***

Whole protein formulae are generally recommended (C). More concentrated high-energy formulae are preferable in patients with ascites in order to minimise fluid overload (C).

BCAA-enriched formulae should be used in patients with hepatic encephalopathy arising during EN (A).

Oral BCAA supplementation can improve clinical outcome in advanced cirrhosis (B).

If patients are not able to maintain adequate oral intake from normal food, ONS (C) or TF (A) (even in the presence of oesophageal varices) are recommended.

Placement of PEG is associated with a higher risk of complications, due to ascites or varices, and is not recommended (C).

An energy intake of 35–40 kcal/kgBW/d (147–168 kJ/kgBW/d) and a protein intake of 1.2–1.5 g/kgBW/d are recommended (C).

Comment: The available data suggest that ensuring a quantitatively adequate nutrient intake should be the primary goal.[3,5,7,8,29–31] Until recently, it remained unclear whether a formula enriched in branched chain amino acids (BCAA) is superior to a standard whole protein formula, since the issue had only been investigated in a highly selected group of protein intolerant LC patients with encephalopathy.[32] Findings from one older uncontrolled and two recent randomised trials including 174 and 646 patients suggest that long-term (12 and 24 months) nutritional supplementation with oral BCAA granulate as ONS is useful in slowing the progression of hepatic failure and prolonging event-free survival[33–35] (Ib).

Regarding the method of nutritional intervention, nutritional counselling alone[29] or in combination with ONS[3,5,31] will often prove successful. If energy requirements cannot be met, TF is required.[7,8,30] Reservations concerning the placement of nasogastric tubes because of their potential to provoke gastrointestinal bleeding are not supported by the current literature[7–9] (Ib). Ascites, impairment of the coagulation system and porto-systemic collateral circulation due to portal hypertension have been reported as contraindications to PEG placement.[36]

Available data on energy and protein requirements are surveyed and appropriate recommendations are made in a former ESPEN guideline paper.[22] They are based on the investigation of protein requirement of LC patients[37] and on the amounts of energy and nitrogen given in intervention studies.[3,5–8,30,31] A recently published randomised trial[38] demonstrates that diets containing 1.2 g of protein can safely be administered to patients with LC suffering from episodic encephalopathy and that—even transient—protein restriction does not

confer any benefit to patients during an epsiode of encphalopathy [Ib].

2.4. Does EN improve nutritional status, liver function or prognosis?

EN improves nutritional status and liver function, reduces complications and prolongs survival in LC and is therefore recommended (A).

Comment: This recommendation is based on the results of five randomised trials in 245 patients[5,7,8,29,31] (Ib) of which the majority were alcoholic cirrhotics. It had already been shown in individual trials with small sample size, that in LC patients EN improves liver function,[7,8] nutritional status[29] and survival[7] (Ib). From these trials it appears that a decrease in mortality can be seen most readily when a low protein intake with normal food in the control group is compared with a high protein intake in the intervention group.[37] After successful treatment of portal hypertension by transjugular intrahepatic stent-shunt (TIPS), LC patients on normal food (according to ESPEN recommendations) were able to improve their body composition.[39,40]

3. Transplantation and surgery

(See also guidelines "Surgery incl. Organ Transplantation").

3.1. Does nutritional status influence outcome? Which is the best widely applicable method of assessing nutritional status?

The prognostic value of preoperative nutritional status in liver transplant patients has been demonstrated (Ib).

Simple bedside methods such as SGA or anthropometry are considered adequate to identify patients at risk (C). In order to quantitate undernutrition the determination of phase angle α or body cell mass using BIA is recommended, despite some limitations in patients with ascites (B).

Comment: Data on patients with chronic LD undergoing surgery other than orthotopic liver transplantation are few.

In several descriptive studies higher rates of complications and mortality are reported in patients with preoperative undernutrition who undergo transplantation for terminal chronic LD.[11–13,17–19,41] Undernourished LC patients are at higher risk of postoperative complications including higher mortality following abdominal surgery.[42]

In order to identify undernutrition, simple bedside methods such as SGA or anthropometry are quite adequate. As a prognostic indicator, the combination of decreased BCM (less than 35% of actual body mass as assessed by BIA) and hypermetabolism[20,43] has received the most systematic evaluation. Hypermetabolism, however, can only be assessed by indirect calorimetry, which is not available in all hospitals. The use of other composite scores confers no additional prognostic value.[22]

3.2. When is EN indicated or contraindicated?

Preoperative patients: As recommended for LC patients.

Postoperative patients: After liver transplantation, normal food and/or EN should be initiated within 12–24 h postoperatively (B).

After other surgical procedures, patients with chronic LD should receive early normal food or EN like other patient groups (B). Postoperative nutrition yields superior results to the infusion of fluid and electrolytes only (Ib).

Organ donors: No specific recommendations can be made with regard to optimal organ donor conditioning.

Comment: *Preoperative patients*: Although the prognostic relevance of undernutrition in transplant candidates has been demonstrated, it has not yet been shown that preoperative nutritional intervention improves clinically relevant outcomes. In patients with less advanced and predominantly cholestatic LC, there was no advantage of ONS over nutritional counselling and normal food[29] (Ib).

Postoperative patients: Postoperative nutrition in transplant recipients is superior to the infusion of fluid and electrolytes only with regard to time on the ventilator and length of stay in ICU[44] (Ib). EN started as early as 12 h after the operation is associated with a lower rate of infections than parenteral nutrition[45] (Ib).

LC patients have a reduced rate of complications and improved nitrogen economy after abdominal surgery if they receive nutritional support instead of just fluid and electrolytes[46–48] (Ib). It may safely be assumed that EN in the early postoperative period yields even better results; however no studies have compared the two regimens in LC. There are data to suggest a beneficial effect on gut permeability of sequential parenteral nutrition/EN (via jejunostomy) as compared to parenteral nutrition alone or no postoperative nutrition at all[48] (Ib).

Fatty liver is known to be a risk factor for primary graft malfunction. No data are available addressing the role of nutritional management of the organ donor.

3.3. How should EN be delivered?

- ***Which formula?***
- ***Which method of delivery?***
- ***What dosage?***

Preoperative patients: For adults, the recommendations for LC are applicable. For children awaiting transplantation, the administration of BCAA-enriched formulae should be considered (B, one randomised trial).

Postoperative patients: Whole protein formulae are generally recommended (C). Concentrated high-energy formulae are preferable in patient with ascites for reasons of fluid balance (C).

BCAA-enriched formulae should be used in patients with hepatic encephalopathy arising during EN (A).

For early EN the use of nasogastric tubes or catheter jejunostomy is recommended as in non-LD surgery (B) (see also guidelines "Surgery incl. Organ Transplantion").

An energy intake of 35–40 kcal/kgBW/d (147–168 kJ/kgBW/d) and a protein intake of 1.2–1.5 g/kgBW/d are recommended (C).

Comment: *Preoperative patients*: For adult patients the recommendations for LC apply. Paediatric transplant patients with predominantly cholestatic LD show a better increase in BCM if they receive BCAA-enriched formula[49] (Ib).

Postoperative patients: There are few studies addressing this topic. Whole protein formulae with[50] or without pre- and probiotics[45,51] or peptide-based formulae via catheter jejunostomy[52,53] have been used for early EN of adult liver transplant recipients. Formulae were administered via nasogastric or nasoduodenal tubes after endoscopic placement[51] or via catheter jejunostomy[48,52,53] placed during laparotomy.

3.4. Does EN improve nutritional status, liver function, and prognosis?

Preoperative patients: An improvement in perioperative mortality or complication rate by preoperative TF or ONS has not yet been shown. However, a clear recommendation for nutritional therapy in undernourished LC patients is supported by the statements concerning nutrition in LC made in statement 2.4 (C).

Postoperative patients: Early normal food or EN is recommended for transplant and surgery patients with LC in order to minimise perioperative—in particular infectious—complications (B).

Comment: *Preoperative patients*: ONS improve anthropometric variables and muscle function, but not overall survival after transplantation, when compared with normal food combined with nutritional counselling.[29] Since normal food and nutritional counselling lead to the same adequate intake as when ONS are added, both regimens are considered similarly effective (or ineffective). Moreover, in this study there was no control group without any intervention, since that would have been unethical on the basis of current knowledge.

Postoperative patients: Transplant patients who received early EN 12 h after surgery developed fewer viral infections and had better nitrogen retention[45] (Ib). In comparison with parenteral nutrition, EN reduces complication rates and costs in transplant patients[51] (Ib).

4. Fulminant liver failure

Fulminant liver failure without treatment results in death within days. Stabilisation of metabolism is mandatory and, in that phase of the disease, it is more important than nutritional therapy aimed at meeting daily requirements. Hypoglycaemia is a frequent metabolic disturbance and merits particular attention and therapy, such as (par)enteral glucose administration (C).

Patients with acute liver failure should receive EN via nasoduodenal tube (C). No recommendations concerning a disease specific composition of enteral formulae can currently be given (C).

The recommended amount of enteral formula is based on the dosage in critical illness (III). Due to severe liver failure, glucose, lactate, triglycerides and ammonia plasma levels should be monitored closely and used as surrogate markers of substrate utilisation (C).

Comment: The scant available data preclude any clear recommendation. In recognition of this deficit, a survey was carried out in European hepatology centres on issues of parenteral nutrition in patients with fulminant liver failure.[54] One important result was that centres with a high caseload favour nasoduodenal TF, which could be carried out successfully in the majority of cases.

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