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ESPEN Guideline

ESPEN practical guideline: Clinical nutrition in liver disease

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SUMMARY

Background: The Practical guideline is based on the current scientific ESPEN guideline on Clinical Nutrition in Liver Disease.
Methods: It has been shortened and transformed into flow charts for easier use in clinical practice. The guideline is dedicated to all professionals including physicians, dieticians, nutritionists and nurses working with patients with chronic liver disease.
Results: A total of 103 statements and recommendations are presented with short commentaries for the nutritional and metabolic management of patients with (i) acute liver failure, (ii) alcoholic steatohepatitis, (iii) non-alcoholic fatty liver disease, (iv) liver cirrhosis, and (v) liver surgery/transplantation. The disease-related recommendations are preceded by general recommendations on the diagnostics of nutritional status in liver patients and on liver complications associated with medical nutrition.
Conclusion: This practical guideline gives guidance to health care providers involved in the management of liver disease to offer optimal nutritional care.

1. Introduction

It is well-known that nutrition has a central prognostic and therapeutic role in the management of patients with liver disease. Therefore, ESPEN produced scientific guidelines on this topic since 1997. To improve implementation and dissemination of these guidelines into clinical practice, a shortened version has been created based on the most recent ESPEN guideline on clinical nutrition in liver disease [1]. Apart from shortening the commentaries, we have grouped the recommendations differently according to the five major liver diseases with a strong relation to nutrition including acute liver failure (ALF), alcoholic and non-alcoholic steatohepatitis (ASH and NASH), liver cirrhosis, liver transplantation (LTx) and other surgery. Moreover, we supplemented the text with flow charts to support guidance in nutritional therapy and to allow online versions of the guideline such as an app and a web version (Fig. 1). This guideline is aimed to address clinically relevant issues in the nutritional and metabolic management of adult patients with liver disease. Target users of the guideline are health care providers involved in the care of patients with liver disease, e.g. medical specialists involved in the management of liver disease, family physicians, pharmacists, nurses, dieticians, nutritionists, as well as by medical leaders and administrators of liver units.

2. Methodology

The present practical guideline consists of 85 recommendations and 17 statements, all based on the current ESPEN Guideline on clinical nutrition in liver disease [1]. The original guideline was shortened by restricting the commentaries to the gathered

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Abbreviations

ALF	acute liver failure
ASH	alcoholic steatohepatitis
BCAA	branched chain amino acids
CT	computed tomography
DXA	dual energy X-ray absorptiometry
EN	enteral nutrition
ICU	intensive care unit
IFALD	intestinal failure associated liver disease
LTx	liver transplantation
MCT	medium-chain triglyceride
MedD	Mediterranean diet
MRT	magnetic resonance tomography
NAFL	non-alcoholic fatty liver
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
ONS	oral nutritional supplements
PEG	percutaneous endoscopic gastrostomy
PN	parenteral nutrition
PNAC	parenteral nutrition-associated cholestasis
PNALD	parenteral nutrition associated liver disease
REE	resting energy expenditure

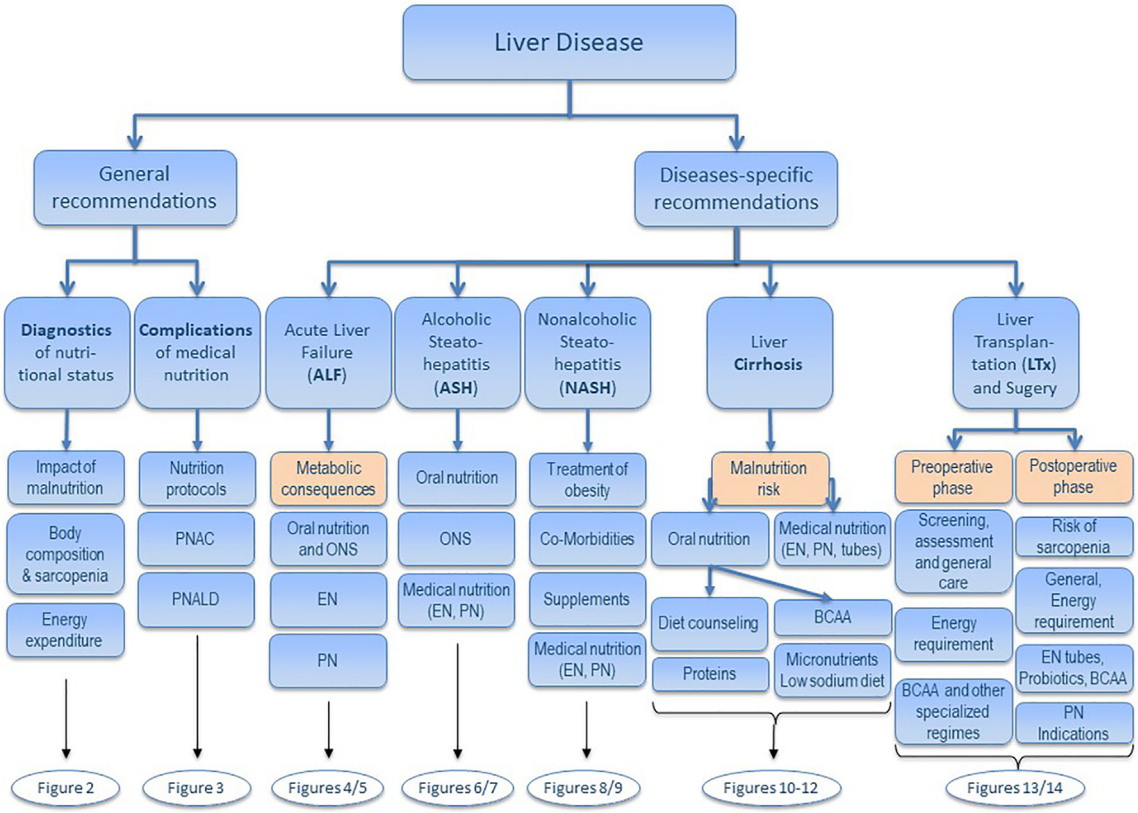

Fig. 1. Structure of the ESPEN practical guideline: "Clinical nutrition in liver disease".

evidence and literature on which the recommendations are based on. The recommendations were not changed, but the recommendations and statements were re-ordered and grouped to disease entities. Most relevant, presentation of the content was transformed into a graphical presentation consisting of decision-making flow charts wherever possible. The original guideline was developed according to the standard operating procedure (SOP) for ESPEN guidelines [2]. This SOP is oriented on the methodology of the Scottish Intercollegiate Guidelines Network (SIGN). Literature was searched and graded into 1–4 according to evidence, and recommendations were created and graded into four classes (A/B/0/GPP). All recommendations were not only based on evidence, but also underwent a consensus process, which resulted in a percentage of agreement (%). Whenever possible, representatives from different professions (physicians, dieticians, nurses, others) as well as patient representatives were involved. The guideline process was funded exclusively by the ESPEN society. The guideline shortage and dissemination was funded in part by the UEG society, and also by the ESPEN society. For further details on methodology, see the full version of the ESPEN guideline [1] and the ESPEN SOP [2].

2.1. General recommendations

2.1.1. Diagnostics of nutritional status (Fig. 2)

2.1.1.1. Impact of nutrition

1) **Malnutrition can impair the whole spectrum of hepatic metabolic functions. Malnutrition alone can cause severe fatty liver but is not known to cause chronic liver disease. (Statement 14, strong consensus 100%)**

Severe malnutrition in children can cause fatty liver which in general is fully reversible upon refeeding. In children with

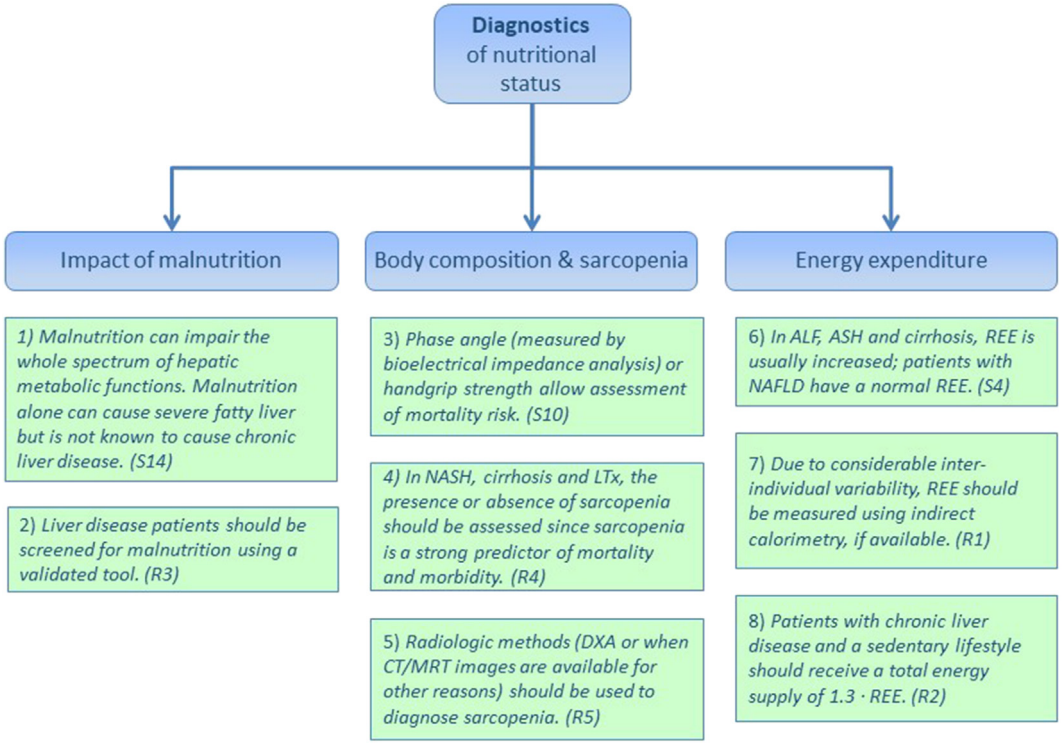

Fig. 2. Diagnostics of nutritional status in liver disease (ALF, acute liver failure; ASH, alcoholic steatohepatitis; CT, computed tomography; DXA, dual energy X-ray absorptiometry; LTx, liver transplantation; MRT, magnetic resonance tomography; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic fatty liver disease; REE, resting energy expenditure).

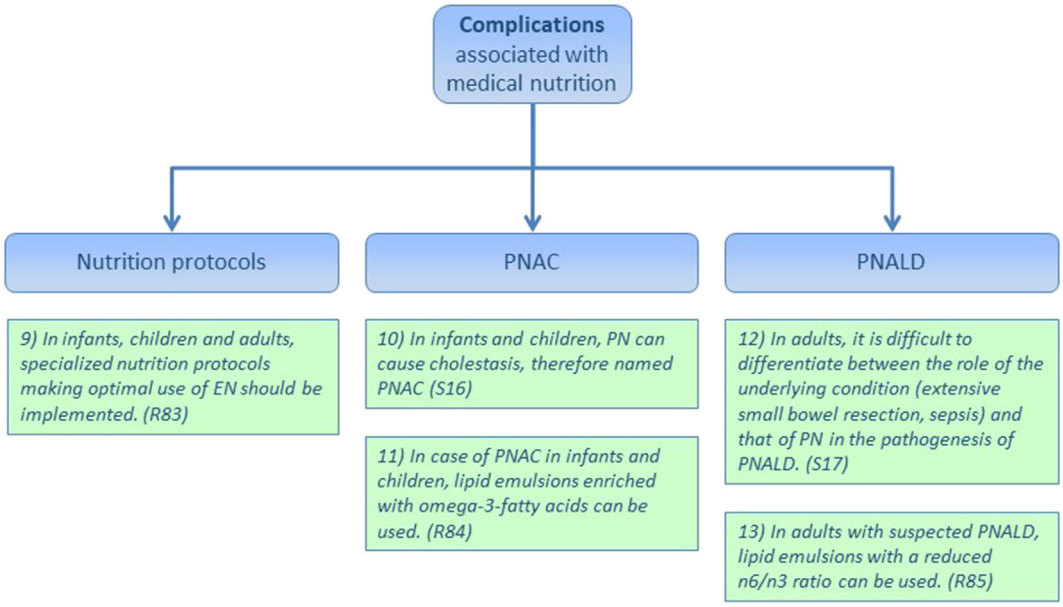

Fig. 3. Complications associated with medical nutrition in liver disease (EN, enteral nutrition; PN, parenteral nutrition; PNAC, parenteral nutrition associated cholestasis; PNALD, parenteral nutrition associated liver disease).

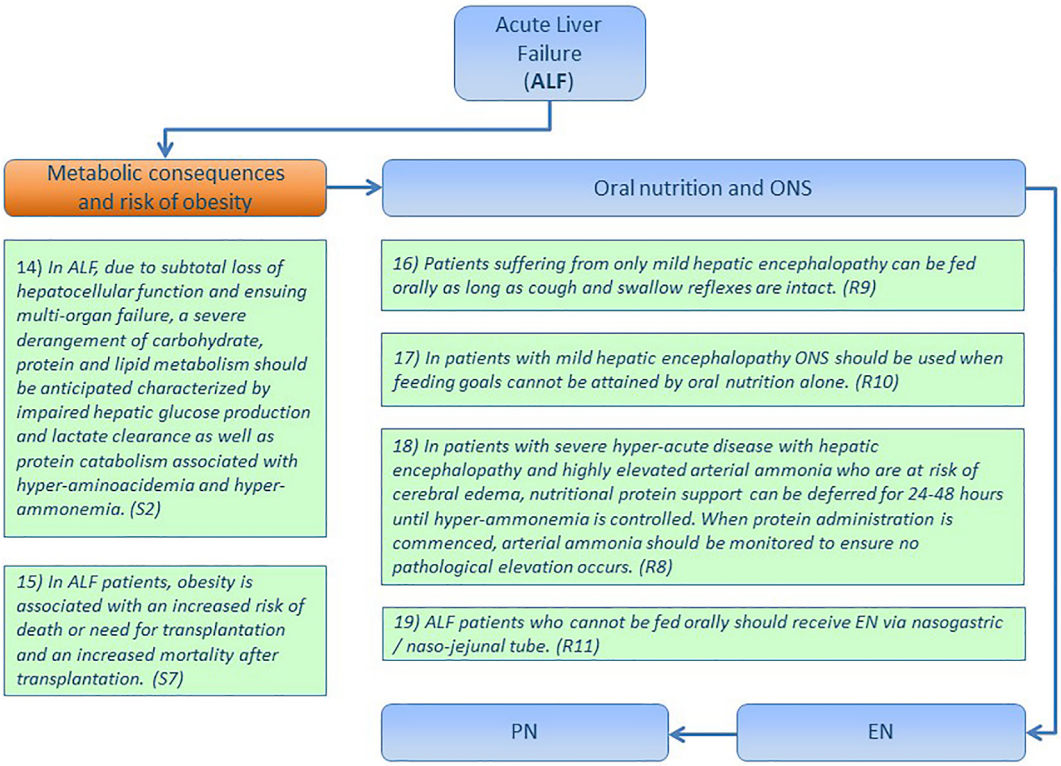

Fig. 4. Clinical nutrition in acute liver failure part 1 (ALF, acute liver failure; EN, enteral nutrition; ONS, oral nutritional supplements; PN, parenteral nutrition).

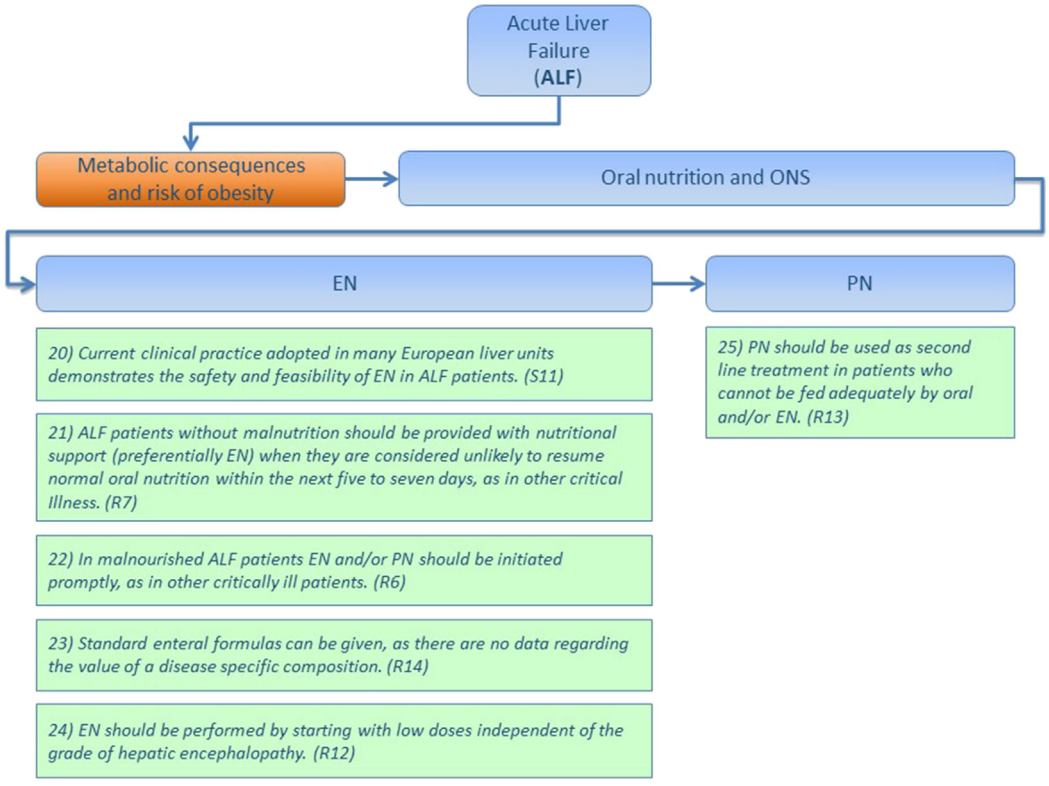

Fig. 5. Clinical nutrition in acute liver failure part 2 (ALF, acute liver failure; EN, enteral nutrition; ONS, oral nutritional supplements; PN, parenteral nutrition).

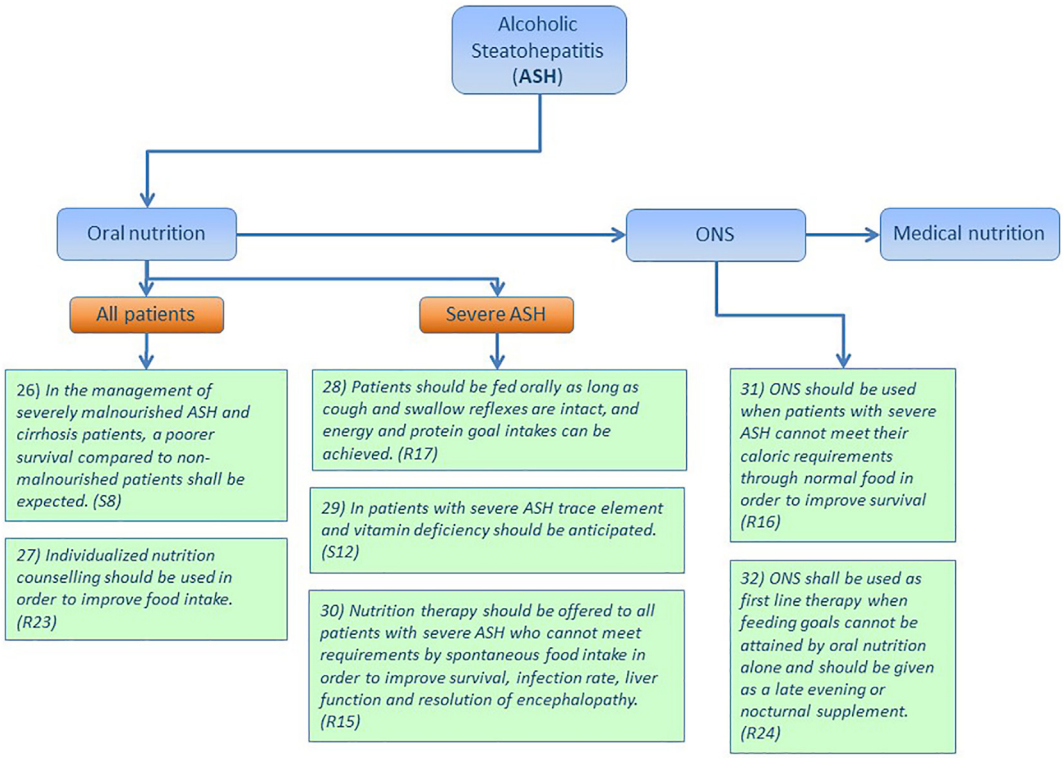

Fig. 6. Clinical nutrition in alcoholic steatohepatitis part 1 (ASH, alcoholic steatohepatitis; ONS, oral nutritional supplements).

Kwashiorkor, there seems to be a maladaptation associated with less efficient breakdown of fat and oxidation of fatty acids compared to children with marasmus. An impairment of fatty acid removal from the liver could not be observed.

2) **Liver disease patients should be screened for malnutrition using a validated tool. (Recommendation 3, grade B, strong consensus 93%)**

NRS-2002 and MUST are validated tools to screen hospitalized patients for risk of malnutrition [3,4] and are recommended by ESPEN. The Royal Free Hospital Nutrition Prioritizing Tool has been developed as a screening tool for malnutrition in liver disease patients. In a head-to-head comparison, the Royal Free Hospital Nutrition Prioritizing Tool was more sensitive than the NRS-2002 to identify liver patients at risk for malnutrition [5]. NRS-2002 was considered helpful in identifying malnourished cirrhosis patients with hepatocellular carcinoma [6]. According to a recent review, none of the available screening tools has been validated rigorously in cirrhosis patients leaving the Royal Free Hospital Nutrition Prioritizing Tool as the best option currently available [7].

2.1.1.2. Body composition and sarcopenia

3) **Phase angle (measured by bioelectrical impedance analysis) or handgrip strength allow assessment of mortality risk. (Statement 10, strong consensus 93%)**

Handgrip strength is a good predictor of the rate of complications within the next year [8]. Handgrip strength appears a valuable tool to measure efficacy of nutritional intervention [9]. Reactance and resistance readouts from BIA can be used to calculate phase angle or body cell mass as a measure of cell mass and cell function for the nutritional assessment. In liver cirrhosis, low phase angle is associated with increased mortality as in many other disease entities [10].

4) **In NASH, cirrhosis and LTx, the presence or absence of sarcopenia should be assessed since sarcopenia is a strong predictor of mortality and morbidity. (Recommendation 4, grade B, strong consensus 100%)**

In cirrhosis patients on the transplant wait list, impaired muscle function in terms of 6-min walk distance, grip strength and the short physical performance battery but not loss of muscle mass in terms of computed tomography (CT) derived skeletal muscle index was associated with increased mortality [11]. In cirrhosis patients, frailty experienced as a functional decline in grip strength, gait speed, chair stands or short physical performance battery has been shown associated with increased risk for complications requiring hospitalization [12] or death on the wait list or delisting [13,14].

5) **Radiologic methods (dual energy X-ray absorptiometry (DXA) or when CT/magnetic resonance tomography (MRT) images are available for other reasons) should be used to diagnose sarcopenia. (Recommendation 5, grade B, strong consensus 100%)**

Sarcopenia is the key feature of malnutrition in cirrhosis patients and can be assessed by radiologic methods (DXA, CT) to detect loss of muscle mass or by tests of muscle function such as exercise test or 6-min walk distance. Sarcopenia can be diagnosed when there is loss of muscle mass or muscle function. On CT images at the level of lumbar vertebra 3 [15] or lumbar vertebra 4 [16] skeletal muscle area can be measured and normalized for stature.

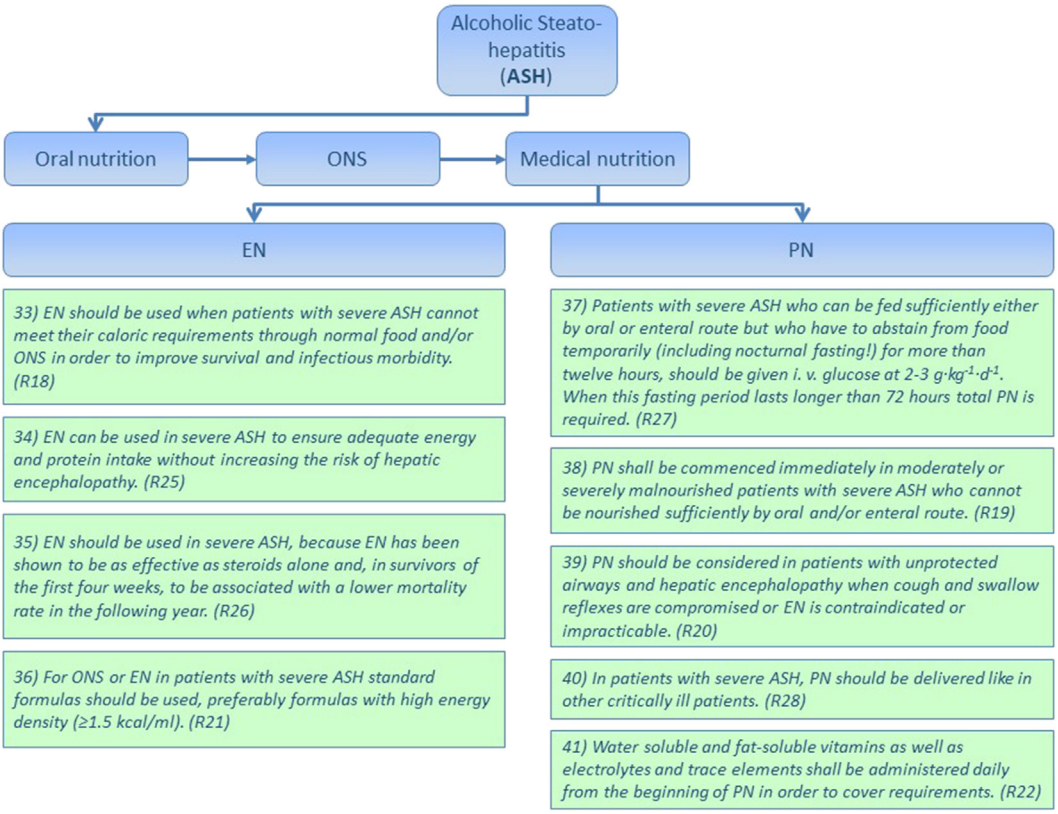

Fig. 7. Clinical nutrition in alcoholic steatohepatitis part 2 (ASH, alcoholic steatohepatitis; EN, enteral nutrition; ONS, oral nutritional supplements; PN, parenteral nutrition).

The skeletal muscle area at L3 has been shown to be linearly correlated with whole body muscle mass [17]. Loss of skeletal muscle mass on CT has been associated with increased mortality in cirrhosis patients [15,16,18], obese cirrhosis patients [19], cirrhosis patients wait listed for transplantation [20] and in orthotopic liver transplant recipients [21–23].

2.1.1.3. Energy expenditure

6) **In ALF, ASH and cirrhosis, resting energy expenditure (REE) is usually increased; patients with non-alcoholic fatty liver disease (NAFLD) have a normal REE (Statement 4, consensus 90%)**

Studies in ALF patients using indirect calorimetry showed an increase in REE by 18% or 30%, respectively, in comparison with healthy controls [24,25]. Therefore, in terms of REE, patients with ALF are not different from critically ill patients with other etiologies. In ASH patients, the relationship between measured and predicted REE was not different from healthy individuals or patients with liver cirrhosis. However, when related to their reduced muscle mass REE in ASH patients was clearly higher than that in healthy controls. In alcoholics without biochemical evidence of liver disease but not in patients with alcoholic cirrhosis an increased REE (25.8 vs 20.8 kcal·kg^{-1}·d^{-1}) was observed [26]. Likewise, in alcoholics with fatty liver, ASH or cirrhosis excessive alcohol consumption was associated with increased REE (26%). In NAFLD/NASH, it is difficult to draw a clear picture, because patient populations studied vary according to the presence or absence of overweight/obesity, chronic inflammation, or the metabolic syndrome.

7) **Due to considerable inter-individual variability, REE should be measured using indirect calorimetry, if available. (Recommendation 1, grade GPP, strong consensus 100%)**

Whenever available, indirect calorimetry should be used to measure REE, since in an individual patient measured REE may differ considerably from estimated values [27]. Measured REE is higher than predicted in up to 35% of cirrhotic patients (hypermetabolism), and below the predicted value in 18% of the patients [28,29]. In liver cirrhosis hyper-metabolism was associated with reduced event-free survival and unfavorable outcome after transplantation [28,30] and seems to regress with improvement of body composition [31]. As a less expensive, valid and rapid method hand-held calorimetry has been proposed [32]. Hand-held calorimeters only measuring oxygen consumption and calculating energy expenditure assuming a respiratory quotient of 0.85 are more accurate than predictive equations for determining REE.

8) **Patients with chronic liver disease and a sedentary lifestyle should receive a total energy supply of 1.3 x REE. (Recommendation 2, grade B, consensus 81%)**

Estimates of total energy expenditure (32 kcal·kg^{-1}·d^{-1}) indicate that the 24 h energy requirement of cirrhosis patients amounts to about 1.3 · measured REE (24 kcal·kg^{-1}·d^{-1}) [33,34]. Diet-induced thermogenesis and the energy cost of defined physical activity in stable cirrhosis patients also show no deviation from values obtained in healthy individuals. However, the level of spontaneous physical activity is considerably lower in patients with cirrhosis. It is likely that the increased energy requirement in advanced illness is balanced by diminished physical activity reflecting the poor physical condition. In cirrhotics without ascites,

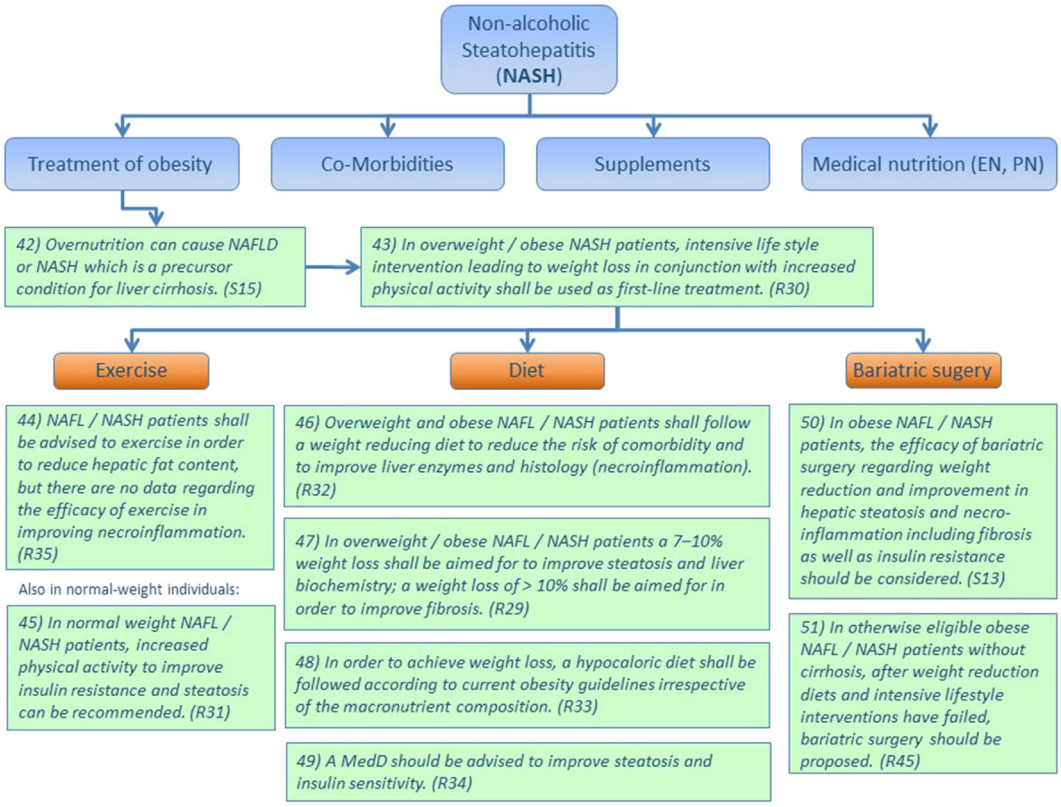

Fig. 8. Clinical nutrition in non-alcoholic steatohepatitis part 1 (EN, enteral nutrition; MedD, Mediterranean diet; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PN, parenteral nutrition).

the actual body weight should be used for the calculation of the basal metabolic rate. In patients with ascites the ideal weight according to body height should be used, despite the report from a series of ten patients with cirrhosis of whom only four were completely evaluated [35] in which it was suggested that ascites mass should not be omitted when calculating energy expenditure. Liver transplant patients on average have similar energy requirements as the majority of patients undergoing major abdominal surgery [36].

2.1.2. Complications associated with medical nutrition (Fig. 3)

2.1.2.1. Nutrition protocols

9) **In infants, children and adults, specialized nutrition protocols making optimal use of EN should be implemented. (Recommendation 83, Grade B, strong consensus 92%)**

In infants and neonates, a number of reports suggest that the institution of specialized nutrition protocols is beneficial in achieving intestinal rehabilitation. Such protocols aim at limiting the infusion of soy-bean based lipid and maximizing oral and enteral stimulation and administering cyclic PN. A retrospective study showed that the implementation of feeding guidelines resulted in decreased times without nutrition, shorter duration of PN support, and significantly fewer infants developed PNALD after guideline implementation [37]. In a multiple-variable analysis septic episodes (odds ratio 3.23), days of lipid >2.5 $g \cdot kg^{-1} \cdot d^{-1}$ (odds ratio 1.04), and 60 days of maximal lipid (odds ratio 10) were found to be the key elements for the development of PNAC [38].

2.1.2.2. PNAC

10) **In infants and children, parenteral nutrition (PN) can cause cholestasis, therefore named PN-associated cholestasis (PNAC). (Statement 16, strong consensus 92%)**

Due to the different features of PNAC in newborns and infants and PN-associated liver disease (PNALD) in adults, PNAC is addressed as an exception in these guidelines on nutrition in adult liver patients. The beneficial effect of specialized nutrition protocols limiting the amount of lipid infused in neonates and infants as well as in adults point to the pathogenic role of PN in the development of cholestasis (see also points 11–13). A second independent factor causing liver damage is the extent of loss of intestinal mass as shown in the seminal paper by Stanko and colleagues showing an association between liver injury and extent of gut resection but not PN [39]. Thus, intestinal failure-associated liver disease (IFALD) and PNALD are difficult to separate in the individual patient and occur in up to 60% of infants and up to 85% of neonates who require long-term PN for intestinal failure [40,41]. Whereas adults are more likely to develop steatosis only, infants and neonates are more susceptible to hepatocellular injury or cholestasis, probably due to immature bile metabolism and transport. This is reflected in the term PNAC that is frequently used in the pediatric literature [42], whereas the term PNALD has been used in both adult and pediatric patients. In infants and neonates, mortality is high, up to 40%, and PNAC has become a major indication for pediatric LTx [42]. In adults, the incidence of advanced IFALD/PNALD ranges from 0% to 50% and mortality ranges from 0% to 22% [41]. Progressive IFALD/

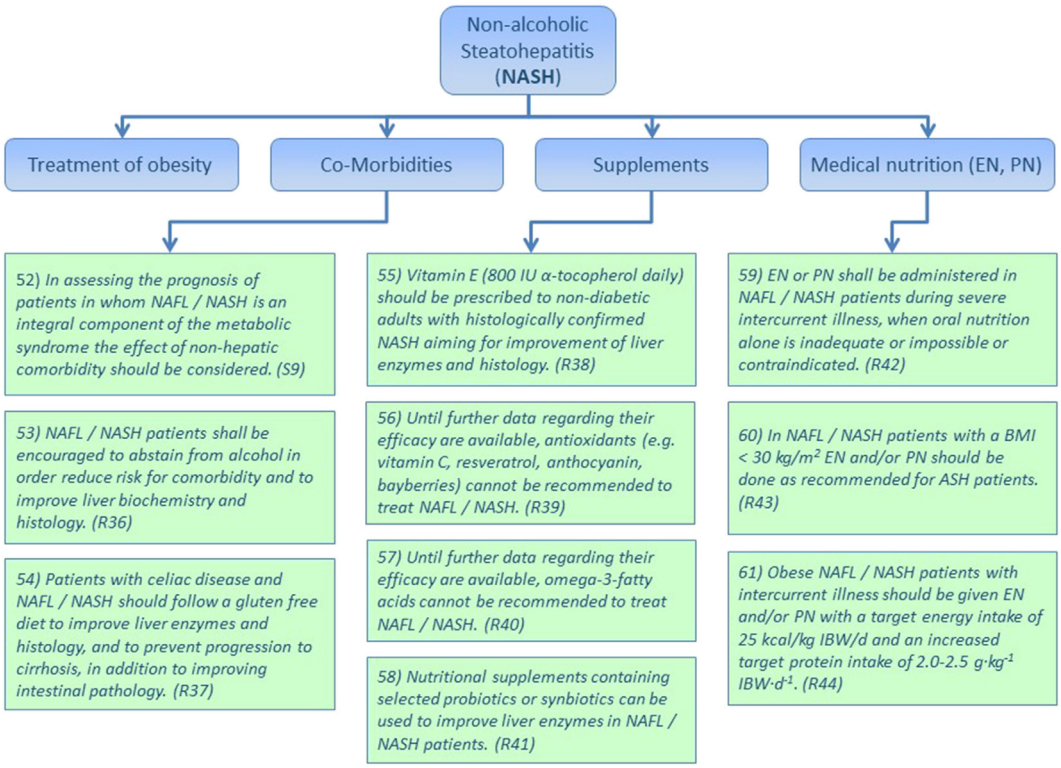

Fig. 9. Clinical nutrition in non-alcoholic steatohepatitis part 2 (EN, enteral nutrition; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PN, parenteral nutrition).

PNALD is an accepted indication for a timely life-saving small bowel transplantation [43].

11) **In case of PNAC in infants and children, lipid emulsions enriched with omega-3-fatty acids can be used. (Recommendation 84, grade 0, strong consensus 100%)**

Lipid emulsions containing fish oils as the triglyceride source were proposed to be protective in PNAC/PNALD. This has been evaluated in a number of publications in which a 100% fish-oil emulsion was infused at a rate limited to 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ whereas the soy-bean emulsion was given at rates up to 4.0 $g \cdot kg^{-1} \cdot d^{-1}$ and thus, it cannot be excluded that the quantity of lipid infused rather than its composition determined the observed improved outcome [44,45]. In a retrospective analysis of 51 pediatric PNALD patients with cirrhosis the use of a fish-oil based lipid emulsion was accompanied by a resolution of cholestasis in 76% [46]. A randomized controlled trial comparing a 100% fish-oil emulsion with a soy-bean lipid emulsion both at a dose of 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ was terminated early because of an unexpectedly low incidence of PNAC [47]. No patient developed fatty acid deficiency and both regimens were well tolerated and safe.

In a different approach, the reduction of soy-bean based lipid has been achieved by adding a fish-oil emulsion [48], or using lipid emulsions consisting of a mixture of either soy-bean based lipid and medium-chained triglyceride (MCT)-lipid [49], or a mixture of a fish-oil emulsion and a soy-bean olive-oil emulsion [50], or soy-bean based lipid and olive oil and MCT-lipid and fish-oil [49]. In randomized controlled trials comparing a SMOF (soy-bean based lipid and olive oil and MCT-lipid and fish oil) emulsion with a soy-bean based emulsion the fish-oil containing SMOF emulsion proved to be safe and more effective in reducing bilirubin levels or oxidative stress [51].

2.1.2.3. PNALD

12) **In adults, it is difficult to differentiate between the role of the underlying condition (extensive small bowel resection, sepsis) and that of PN in the pathogenesis of PNALD. (Statement 17, strong consensus, 100%)**

Cholestatic liver injury occurs in about 50% of patients on long-term home PN. In 1985, Bowyer and colleagues [52] described steatohepatitis in nine out of 60 patients on long-term PN. Liver injury persisted for a median of 15 months and progressed to cirrhosis in three patients. Stanko and colleagues [39] studied adults who had been on PN for one year. They found normal liver enzymes in those who had no or only modest loss of intestine, while 4/6 patients with massive loss of intestine developed progressive cholestasis and steatohepatitis four to ten months after the initiation of PN. Their observation demonstrated that liver injury can occur not only as a sequel of PN – termed PNALD – but also by intestinal failure – termed IFALD. In clinical practice a clear distinction between IFALD or PNALD more often than not is difficult. The pathogenesis of IFALD/PNALD is thought to be multifactorial including factors like disturbance of enterohepatic bile acid cycling, systemic infection, bacterial overgrowth, absence of enteral nutrients and composition of PN. Both lack and excess of specific components of PN are being discussed as causal for PNALD. The fatty acid composition of lipid emulsions as well as choline deficiency, and manganese toxicity have been linked to the occurrence of hepatic steatosis and cholestasis in adults and children.

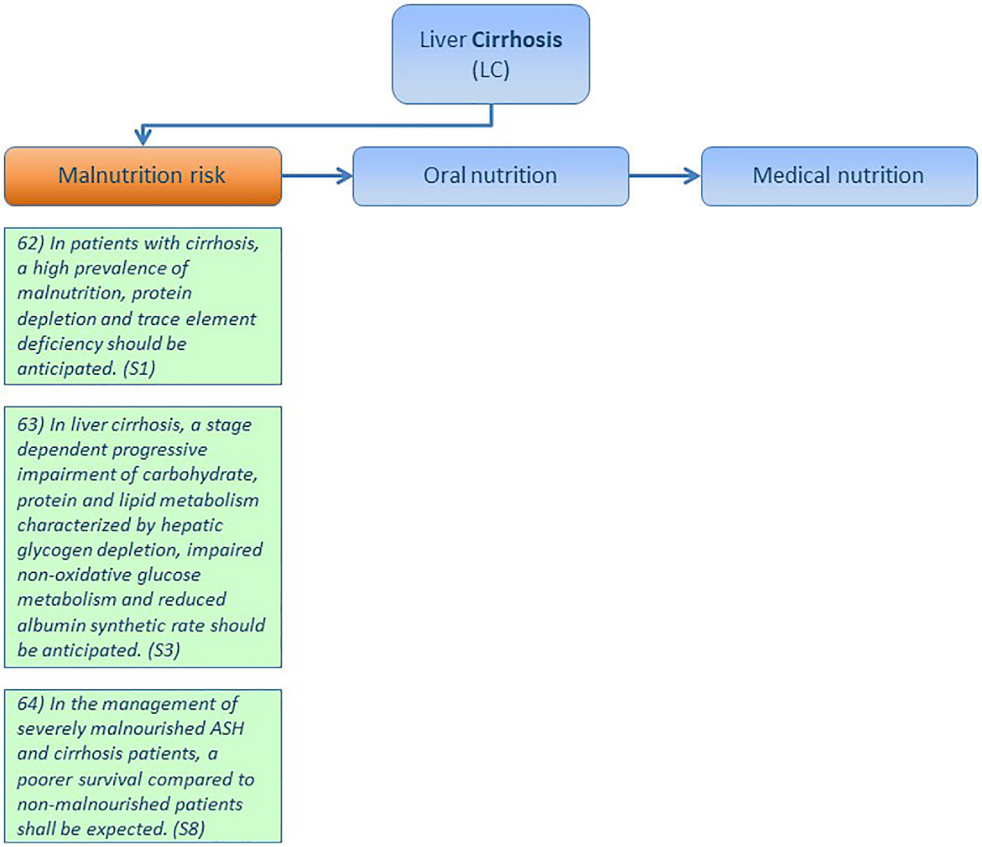

Fig. 10. Clinical nutrition in liver cirrhosis part 1 (LC, liver cirrhosis).

13) **In adults with suspected PNALD, lipid emulsions with a reduced n6/n3 ratio can be used. (Recommendation 85, grade 0, strong consensus 92%)**

In adults, limited data is available regarding the effect of modifying quantity and/or composition of parenteral lipids in the course of PNALD. Limiting soy-bean based lipid to $\leq 1.0\ g \cdot kg^{-1} \cdot d^{-1}$ has been suggested also in adults [53]. The exchange of soy-bean based lipids by a 100% fish-oil emulsion has been reported effective in PNALD [54,55]. In a series of 15 patients, the addition of a fish-oil emulsion to a soy-bean based lipid emulsion was associated with the reversal of a biopsy-proven PNALD [56]. In one case, the use of a fish-oil emulsion together with an olive-oil based PN regimen was associated with a reduction in liver steatosis and inflammation [57]. Taken together, more data are needed before the routine use of fish-oil containing fat emulsions can be recommended for the treatment of PNALD.

2.2. Disease-specific recommendations

2.2.1. Acute liver failure (ALF) (Figs. 4 and 5)

2.2.1.1. Metabolic consequences and risk of obesity

14) **In ALF, due to subtotal loss of hepatocellular function and ensuing multi-organ failure, a severe derangement of carbohydrate, protein and lipid metabolism should be anticipated characterized by impaired hepatic glucose production and lactate clearance as well as protein catabolism associated with hyper-aminoacidemia and hyper-ammonemia. (Statement 2, strong consensus 100%)**

The plasma levels of amino acids are raised 3- to 4-fold in ALF. The amino acid pattern is characterized by a decrease in branched chain amino acids (BCAA) and an increase in tryptophan and aromatic as well as sulphur-containing amino acids. Hypoglycemia is an ominous feature of ALF and is thought to result from (a) a depletion in hepatic glycogen, (b) impaired gluconeogenesis due to loss of hepatocytes, and (c) hyper-insulinemia due to increased secretion and reduced degradation. In ALF, the splanchnic tissues show alteration from net glucose release to net glucose uptake [58]. These changes are accompanied by impaired glucose tolerance, characterized by a 50% decrease in whole body glucose elimination rate, severely decreased (to 15% of controls) insulin sensitivity, and increased glucagon blood levels [59]. In contrast to observations in patients with sepsis, in ALF the splanchnic tissues do not extract but rather release free fatty acids and ketogenesis is reduced [60].

15) **In ALF patients, obesity is associated with an increased risk of death or need for transplantation and an increased mortality after transplantation. (Statement 7, strong consensus 96%)**

In ALF, there is only very limited data available regarding the effect of nutritional status on its course and prognosis. Obese and severely obese had a 1.6- and 1.9-times higher risk of transplantation or death from ALF. Obese patients had a 3.4 times

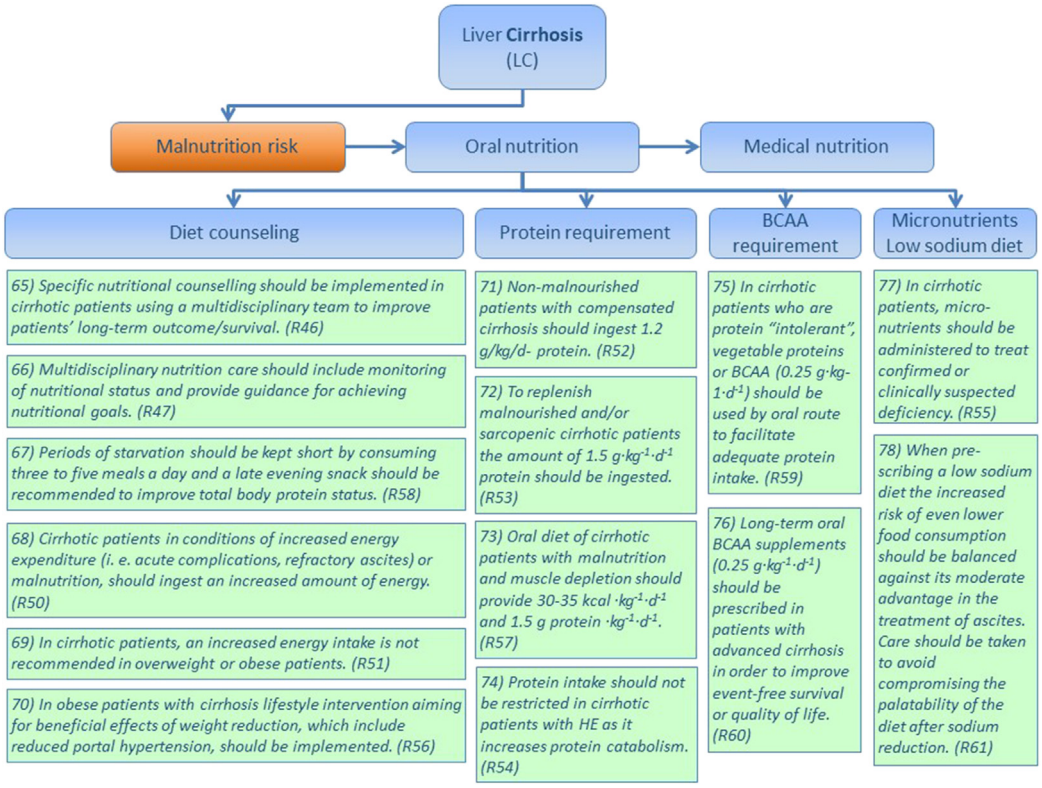

Fig. 11. Clinical nutrition in liver cirrhosis part 2 (BCAA, branched chain amino acids; LC, liver cirrhosis).

higher risk of dying after transplantation. In a small retrospective series, overweight patients were found more susceptible to ALF [61].

2.2.1.2. Oral nutrition and ONS

16) **Patients suffering from only mild hepatic encephalopathy can be fed orally as long as cough and swallow reflexes are intact. (Recommendation 9, grade GPP, strong consensus 100%)**

There are no data from controlled clinical trials in ALF to inform this recommendation.

17) **In patients with mild hepatic encephalopathy oral nutritional supplements (ONS) should be used when feeding goals cannot be attained by oral nutrition alone. (Recommendation 10, grade GPP, consensus 85%)**

There are no data from controlled clinical trials in ALF to inform this recommendation.

18) **In patients with severe hyper-acute disease with hepatic encephalopathy and highly elevated arterial ammonia who are at risk of cerebral edema, nutritional protein support can be deferred for 24–48 h until hyperammonemia is controlled. When protein administration is commenced, arterial ammonia should be monitored to ensure no pathological elevation occurs. (Recommendation 8, grade GPP, consensus 90%)**

Patients with hyper-acute ALF and elevated and sustained arterial ammonia levels (>150 μMol/l) may be at increased risk of cerebral edema and development of intra-cranial hypertension [62,63]. In this specific setting where there may be short-lived but profound impairment of hepatic function, protein administration may further elevate ammonia levels and increase risk of cerebral edema. Its delivery may be deferred for a short period only (24–48 h) as liver function improves and when begun, arterial ammonia should be monitored.

19) **ALF patients who cannot be fed orally should receive EN via nasogastric/naso-jejunal tube. (Recommendation 11, grade GPP, strong consensus 100%)**

According to ESICM guidelines [64] low dose EN should be started when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy. Arterial ammonia levels should be monitored.

2.2.1.3. EN

20) **Current clinical practice adopted in many European liver units demonstrates the safety and feasibility of EN in ALF patients. (Statement 11, strong consensus 100%)**

See commentary to point 19.

21) **ALF patients without malnutrition should be provided with nutritional support (preferentially EN) when they**

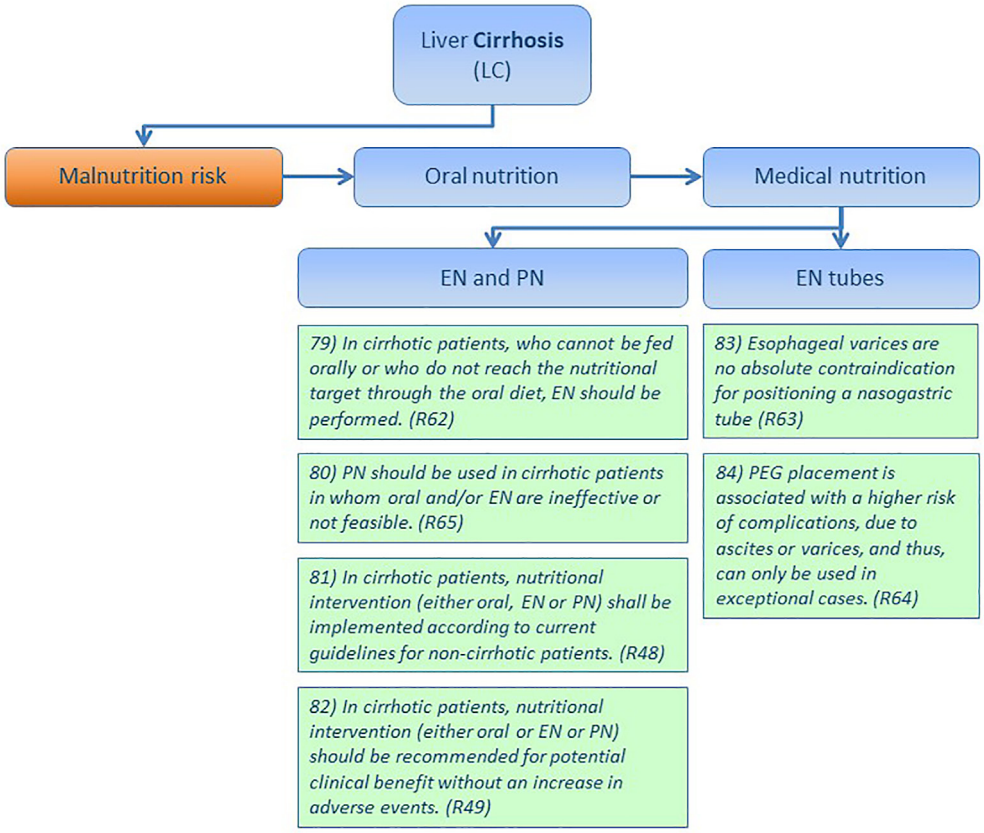

Fig. 12. Clinical nutrition in liver cirrhosis part 3 (EN, enteral nutrition; LC, liver cirrhosis; PEG, percutaneous endoscopic gastrostomy; PN, parenteral nutrition).

are considered unlikely to resume normal oral nutrition within the next five to seven days, as in other critical illness. (Recommendation 7, grade GPP, strong consensus 96%)

See commentary to point 19.

22) **In malnourished ALF patients enteral nutrition (EN) and/or PN should be initiated promptly, as in other critically ill patients. (Recommendation 8, grade GPP, strong consensus 96%)**

In general, decisions on when to initiate nutrition support and which route to use are made in accordance with the recommendations for nutrition support in other ICU patient groups. Three subtypes of ALF can be classified according to their clinical course. In 'hyper-acute' liver failure the onset of hepatic encephalopathy occurs within seven days of the onset of jaundice and patients most often recover promptly with medical therapy alone or after transplantation or die soon after illness onset. Due to the short duration of illness in most patients nutrition support is thought to play a relatively minor role: prognosis is more favorable in this subtype. In 'acute' liver failure the interval between onset of hepatic encephalopathy after the patient became jaundiced is eight days to 28 days and in 'sub-acute' liver failure this interval is between 29 and 72 days. In these latter two subtypes of ALF early nutrition support is more often necessary.

23) **Standard enteral formulas can be given, as there are no data regarding the value of a disease specific composition. (Recommendation 14, grade GPP, strong consensus 100%)**

There are no published studies comparing enteral formulas in patients with ALF. In other critically ill patients, avoidance of the use of all specialty formulas is advised in those in a medical ICU setting, and disease specific formulas in the surgical ICU. There is no evidence that the use of EN enriched with BCAA improves patient outcomes compared to standard whole-protein formulations in other critically ill patients with liver disease, and they are seldom used in the care of ALF patients [65,66].

24) **EN should be performed by starting with low doses independent of the grade of HE. (Recommendation 12, grade GPP, consensus 80%)**

See commentary to point 19.

2.2.1.4. PN

25) **PN should be used as second line treatment in patients who cannot be fed adequately by oral and/or EN. (Recommendation 13, grade GPP, consensus 90%)**

Commentary

There is no trial evidence in patients with ALF to inform these recommendations, and the practice adopted mirrors that in other forms of liver disease and critical illness. In the majority of patients with ALF it is practical and safe to use EN, and formulas can be delivered in amounts comparable to other critical illness. As

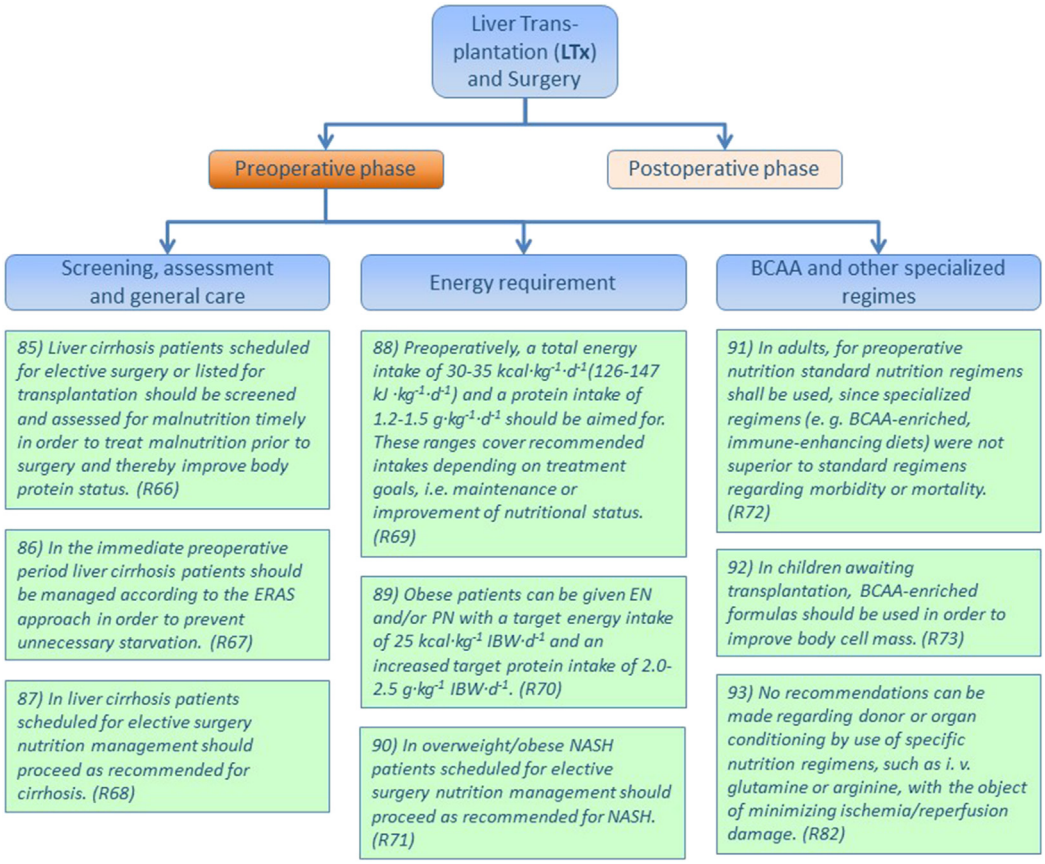

Fig. 13. Clinical nutrition in liver transplantation and surgery part 1 (BCAA, branched chain amino acids; EN, enteral nutrition; ERAS, enhanced recovery after surgery; LTx, liver transplantation; NASH, non-alcoholic steatohepatitis; PN, parenteral nutrition).

documented above (see point 22) a small subgroup of hyper-acute patients may be at transient risk of worsening hyper-ammonemia at high protein loads and thus may be intolerant of full dose EN in the early phase of their illness. In other critically ill patients who require nutrition support therapy, PN carries no clear advantage over EN and may increase infectious complications: the same may be the case in ALF.

2.2.2. Alcoholic steatohepatitis (ASH) (Figs. 6 and 7)

2.2.2.1. Oral nutrition

2.2.2.1.1. All patients

26) **In the management of severely malnourished ASH patients, a poorer survival compared to non-malnourished patients shall be expected. (Statement 8, strong consensus 100%)**

Undernourished ASH patients had a higher rate of morbidity and mortality in the reports of the combined data from the American Veteran Affairs study [67–69]. The Veteran Affairs study data show a clear association between low intake of normal food and high mortality [67] and this finding has been confirmed recently [70].

27) **Individualized nutrition counselling should be used in order to improve food intake. (Recommendation 23, grade GPP, strong consensus 100%)**

There are no studies to evaluate the benefit for individualized nutritional therapy compared to ad lib feeding or nutritional supplementation with 30–35 $kcal \cdot kg^{-1} \cdot d^{-1}$ and 1.2–1.5 $g \cdot kg^{-1} \cdot d^{-1}$ of protein. However, given the suggestions for restriction of sodium, fluid and other substrates depending on co-morbid conditions like renal failure or diabetes mellitus, an individualized, structured nutritional program is likely to be of greater benefit than ad lib feeding.

2.2.2.1.2. Severe ASH

28) **Patients should be fed orally as long as cough and swallow reflexes are intact, and energy and protein goal intakes can be achieved. (Recommendation 17, grade GPP, strong consensus 100%)**

Supplemental feeding in patients with severe ASH is based on nearly universal data that these patients have poor oral intake, lower calorie and protein intake that contribute to mortality and morbidity [67,68]. Therefore, there is compelling rationale to provide sufficient nutrition. However, when adequate oral intake was achieved, there seems to be no specific advantage to the route of administration. In fact, PN was associated with higher risk of complications including infection [71]. There are also advantages to oral feeding of regular diet over EN or PN on gut mucosal integrity and more recent data on maintenance of protective gut microbiome, both of which provide benefits in terms of infection rates that may affect mortality.

29) **In patients with severe ASH trace element and vitamin deficiency should be anticipated. (Statement 12, strong consensus 100%)**

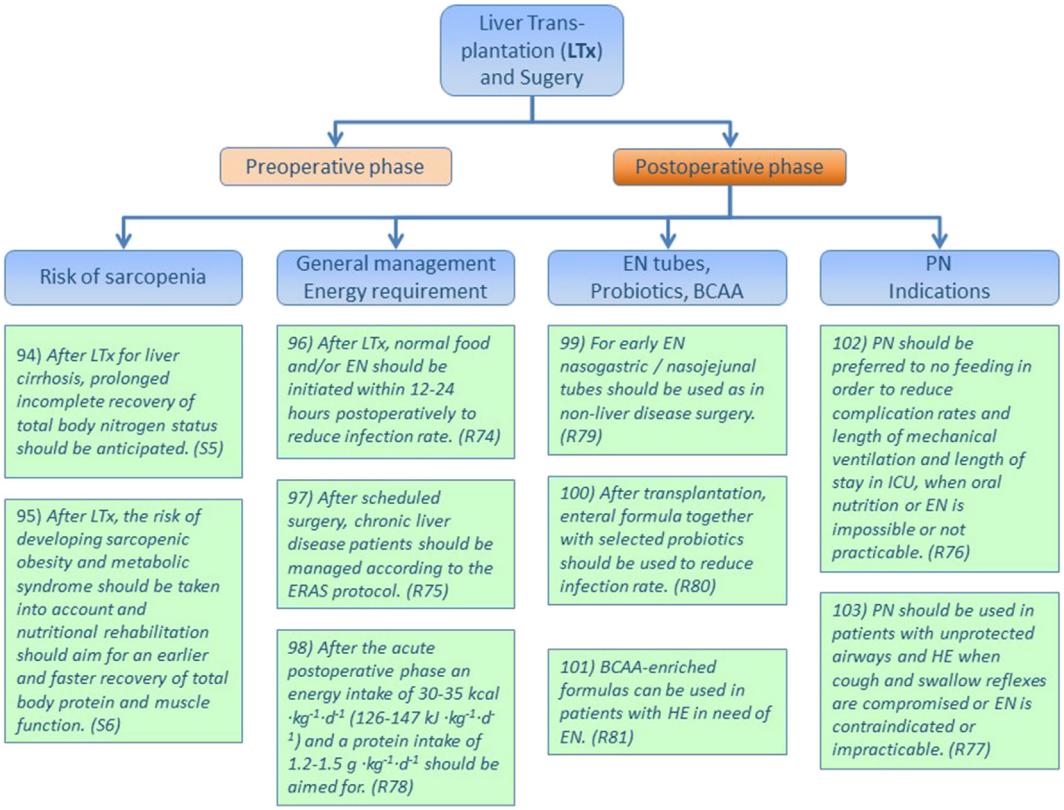

Fig. 14. Clinical nutrition in liver transplantation and surgery part 2 (BCAA, branched chain amino acids; EN, enteral nutrition; ICU, intensive care unit; LTx, liver transplantation; PN, parenteral nutrition).

There are a number of observational studies that show micronutrient deficiencies in patients with alcohol use disorders and alcoholic liver disease and very limited studies in ASH [72–74]. Due to poor oral intake preceding the acute illness, micronutrient deficiency should be expected and replaced in patients with severe ASH. Whether all patients should have malnutrition risk screening or whether there should be universal replacement of micronutrients cannot be answered based on evidence. Based on the frequency of deficiency in B vitamins, zinc and vitamin D, replacement of these may be beneficial. Oral administration of multivitamin and zinc preparations is reasonable in severe ASH because deficiency is frequent and empiric oral supplementation is less expensive than laboratory measurements to establish deficiency before replacing individual micronutrients. Thiamine supplementation is used routinely in clinical practice to prevent Wernicke's encephalopathy and Korsakoff psychosis.

30) **Nutrition therapy should be offered to all patients with severe ASH who cannot meet requirements by spontaneous food intake in order to improve survival, infection rate, liver function and resolution of encephalopathy. (Recommendation 15, grade B, strong consensus 100%)**

Consistent data have shown that malnutrition, defined by a number of measurement tools, is prevalent in the majority (50–100%) of patients with severe ASH [67,68,75]. Presence of malnutrition is an independent predictor of mortality and adversely affects response to corticosteroids and oxandrolone only in moderate but not severe ASH [67,76,77]. In severe ASH, reduced caloric intake is associated with higher mortality and higher complication rates. Oral intake is decreased in these patients and therefore supplementation is necessary to maintain adequate calorie and protein intake. Nutritional supplementation in multiple randomized studies to maintain required caloric intake lowers the incidence of infection and facilitates more rapid resolution of hepatic encephalopathy and improvement in liver function. In the most recent multicenter study, irrespective of treatment, lower calorie intake (21.5 $kcal \cdot kg^{-1} \cdot d^{-1}$) was associated with worse clinical outcomes [70,78]. Calorie intake is significantly reduced even in the abstinent ASH patients, and increased caloric intake improves outcomes [67,79], but there are no randomized controlled trials directly comparing supplemental nutrition alone and ad lib oral intake only that support improved survival for additional nutrition.

2.2.2.2. ONS

31) **ONS should be used when patients with severe ASH cannot meet their caloric requirements through normal food in order to improve survival. (Recommendation 16, grade B, strong consensus 100%)**

In patients with severe alcoholic hepatitis, oral intake is consistently reduced [67,68,75]. When the treatments are consistent in the groups, supplemental nutrition does improve infection and acute mortality, specifically in hospital deaths over ad lib oral dietary intake [80–82]. Enteral or supplemental feeding has been evaluated in severe alcoholic hepatitis, but no mortality benefit has

been consistently reported. However, these data are to be tempered by consistent reports that caloric intake <21.5 kcal·kg^{-1}·d^{-1} was associated with higher mortality [70], there is strong consensus among experts that nutritional supplementation in those patients with poor oral intake should be offered and may provide a survival advantage(80).

32) **ONS shall be used as first line therapy when feeding goals cannot be attained by oral nutrition alone and should be given as a late evening or nocturnal supplement. (Recommendation 24, grade GPP, strong consensus 100%)**

Reduced oral intake is associated with higher mortality and nutritional supplementation is likely to result in more rapid resolution of hepatic encephalopathy and elevated serum bilirubin and lower infection risk, and severe ASH is also a hyper-metabolic state. These data support the use of adequate calorie and protein intake by supplementation. Since compelling data for a late evening snack have been reported in liver cirrhosis including alcoholic cirrhosis [83], it is reasonable to extend these data to support the use of a late evening or nocturnal supplements to reduce the duration of starvation.

2.2.2.3. Medical nutrition

2.2.2.3.1. EN

33) **EN should be used when patients with severe ASH cannot meet their caloric requirements through normal food and/or ONS in order to improve survival and infectious morbidity. (Recommendation 18, grade B, strong consensus 100%)**

When caloric intake is reduced, mortality is higher in severe ASH [70]. Supplementing extra calories does not improve survival in most randomized studies but in patients with malnutrition, lower infection rates were reported [82]. Despite a number of negative studies, the consensus among experts is that in patients with severe ASH who cannot take adequate calories orally, supplemental nutrition may provide a survival advantage, especially in the group with moderate malnutrition [67]. Infection resolution was better with supplemental nutrition, but it is not known if occurrence of new infection is lower. Given that in the non-alcoholic patients with liver disease, poor oral intake and malnutrition are associated with greater risk of infection, one may consider that improved oral intake may lower the risk of infection in severe ASH even though data supporting this contention have not been published.

34) **EN can be used in severe ASH to ensure adequate energy and protein intake without increasing the risk of HE. (Recommendation 25, grade 0, strong consensus 92%)**

EN has proved successful in providing patients with alcoholic cirrhosis [84] or cirrhosis with hepatic encephalopathy grade I-III [85] with adequate nutrition. In one study, ten patients received a BCAA-enriched solution amounting to 70 g protein per day and their mental state improved [85]. In another study 16 patients were given 1.5 g·kg^{-1}·d^{-1} protein using a casein based enteral formula [84]. Likewise, in 136 patients low protein intake was associated with worsening hepatic encephalopathy while patients with a higher protein intake showed improved mental state [86].

35) **EN should be used in severe ASH, because EN has been shown to be as effective as steroids alone and, in survivors of the first four weeks, to be associated with a lower mortality rate in the following year (Recommendation 26, grade B, consensus 85%)**

An randomized study comparing steroids alone with total EN showed no difference in mortality but earlier mortality in steroid treated subjects [78]. Even though mortality in the patients with hepatic encephalopathy was similar in the EN and steroid treated arms, whether the resolution of hepatic encephalopathy was different was not reported [78]. Other studies on EN also reported no survival benefit but EN resulted in greater improvement in hepatic encephalopathy and reduction in bilirubin [84]. Even though the benefit of steroids in severe ASH has been questioned [87], a randomized controlled trial showed that mortality in severe ASH with total EN was similar to that of severe ASH treated with steroids during 28 days. However, patients on EN died sooner and those on steroids died later during treatment for 28 days. Longer-term follow up showed a greater mortality in the steroid treated group related to infection [78]. The authors concluded that a synergistic effect of steroids and EN in severe ASH needs to be evaluated. In a recent study, specifically comparing EN with steroids and conventional nutrition with steroids showed no survival benefit of EN over steroids [70]. However, lower caloric intake did increase mortality in both groups suggesting that EN may provide a survival advantage early in ASH [70,78].

36) **For ONS or EN in patients with severe ASH standard formulas should be used, preferably formulas with high energy density (≥1.5 kcal·ml^{-1}). (Recommendation 21, grade GPP, strong consensus 92%)**

There are no direct studies evaluating specific nutrition protocols in randomized trials in severe ASH. Such protocols include the use of BCAA mixtures, vegetable protein diets, immunonutrition with arginine supplementation. Published data only evaluate intravenous amino acids, commercial parenteral solutions, or intravenous glucose that do not show a mortality benefit in critically ill patients [88]. Immunonutrition was reported to provide no specific therapeutic advantage in a randomized controlled trial in patients undergoing LTx [89]. In severe ASH, there are no controlled trials showing a benefit of specially composed formula over a standard formula. Use of high calorie density supplements can lower fluid administration in patients on fluid restriction. These supplements also lower the duration over which they are administered.

2.2.2.3.2. PN

37) **Patients with severe ASH 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}. When this fasting period lasts longer than 72 h total PN is required. (Recommendation 27, grade GPP, strong consensus 100%)**

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 or nocturnal feeding of ONS was associated with improved protein metabolism in cirrhotic patients [90,91]. There is no corresponding data in patients with severe ASH, but it seems safe to assume that there is a similar depletion in glycogen with all its consequences on protein metabolism in severe ASH patients as well. Therefore, we recommend avoiding fasting patients with severe ASH for more than 12 h and timely institute the infusion of

glucose or peripheral hypocaloric PN. Standard PN in patients who need such an intervention is recommended but mortality is not likely to be improved based on the majority of published data.

38) **PN shall be commenced immediately in moderately or severely malnourished patients with severe ASH who cannot be nourished sufficiently by oral and/or enteral route. (Recommendation 19, grade GPP, strong consensus 100%)**

Nutritional supplementation with amino acid mixtures or calories lowers infection rates and resolution of hepatic encephalopathy but the beneficial effects on survival was only reported in patients with moderate ASH but not in severe ASH [76,77,79,81,82,84]. PN can include amino acids and/or glucose infusion, peripheral or central PN to support dietary intakes in patients whose oral intake is insufficient. Several studies have evaluated different parenteral supplements, mostly amino acid or glucose infusion, seven of which were randomized in ASH. One study showed a survival advantage of intravenous amino acids but this has never been reproduced in any other study [79]. There is limited data on the impact of nutritional intervention alone on hepatic histology in severe ASH. No studies have evaluated progression to cirrhosis, but intravenous amino acids alone or together with glucose were associated with a greater resolution of fatty infiltration [81] or of Mallory hyaline [92]. The improvement or reversal of Mallory hyaline may predict a lower rate of progression. Systematic reviews and meta-analyses also suggest that nutritional supplementation improves rates of resolution of hepatic encephalopathy [81,82].

39) **PN should be considered in patients with unprotected airways and hepatic encephalopathy when cough and swallow reflexes are compromised or EN is contraindicated or impracticable. (Recommendation 20, grade GPP, majority agreement 72%)**

There is no direct evidence evaluating the role of PN in the subgroup of patients with hepatic encephalopathy and/or unprotected airways with impaired protective reflexes. Even though the use of PN in encephalopathic or critically ill patients with impaired cough or gag reflex is recommended by some [93], there are others who do not believe in the use of PN for ASH [94].

40) **In patients with severe ASH, PN should be delivered like in other critically ill patients. (Recommendation 28, grade GPP, strong consensus 100%)**

Even though there are no randomized trials comparing different formulas, rates or components via PN, one can draw some conclusions from the use of PN in critically ill patients. A multidisciplinary team approach is likely to provide benefit and there is no evidence to support a beneficial role for specific nutrient formula in severe ASH. There are no advantages to the type of parenteral solutions used and hence standard practice for PN is recommended in patients with severe ASH.

41) **Water soluble and fat-soluble vitamins as well as electrolytes and trace elements shall be administered daily from the beginning of PN in order to cover requirements. (Recommendation 22, grade GPP, strong consensus 100%)**

In patients with severe ASH, given the nearly universal reduction in dietary intake, there is a high prevalence of micronutrient deficiency that have adverse effects on physiological responses to stress and infection. Hence, vitamins and trace elements shall be given to provide at least the recommended daily amounts. In this high-risk patient group, it seems prudent to administer a first dose of thiamine before commencing PN in order to prevent Wernicke's encephalopathy or refeeding syndrome. Replacement should be considered in all patients on PN even though deficiency may not have been documented. Since PN is likely to be short term, the risk of adverse events due to long term vitamin and micronutrient replacement is low even without quantifying serum concentrations. Specific vitamins, including vitamin A, D and K should be administered along with thiamine, folate and pyridoxine to correct deficiency.

2.2.3. Non-alcoholic steatohepatitis (NASH) (Figs. 8 and 9)

2.2.3.1. Treatment of obesity

42) **Overnutrition can cause NAFLD or NASH which is a precursor condition for liver cirrhosis. (Statement 15, strong consensus 100%)**

The evidence available is reviewed in the following points 43–61 of chapter 2.3 on NASH.

43) **In overweight/obese NASH patients, intensive life style intervention leading to weight loss in conjunction with increased physical activity shall be used as first-line treatment. (Recommendation 30, grade A, strong consensus 100%)**

Life style change resulting in moderate weight loss (<5%) was shown to improve hepatic fat accumulation only when hypocaloric diet and exercise but not when hypocaloric diet alone were implemented [95,96]. Life style change resulting in weight loss of 5–10% was shown to improve histology when hypocaloric diet and exercise were implemented [97–101]. Subgroup analyses indicate that the extent of weight loss seems to be correlated with the extent of histological improvement. Profound improvement of steatosis, inflammation and ballooning was observed already when weight loss of > 7–9% was achieved [97,99,100] while only a weight loss > 10% was associated with improvement in fibrosis [101]. In a systematic trial, shifting energy balance to the same degree by either reduced intake alone or a lesser caloric restriction combined with increased energy expenditure (exercise) yielded the same weight loss (−10%) and the same improvement in hepatic fat, ALT and insulin sensitivity [102]. Readiness for behavior changes, however, is low in overweight/obese patients with NAFLD with only 10% actively working on or preparing to change.

2.2.3.1.1. Exercise

44) **Non-alcoholic fatty liver (NAFL)/NASH patients shall be advised to exercise in order to reduce hepatic fat content, but there are no data regarding the efficacy of exercise in improving necroinflammation. (Recommendation 35, grade A, strong consensus 100%)**

Non-invasive measurements convincingly demonstrate a reduction of intrahepatic and visceral triglycerides in subjects just exercising without losing weight [103–105]. Three months of resistance training improved the hepatorenal-ultrasound index as a readout of hepatic steatosis but did not affect liver enzymes, serum triglycerides or HOMA-IR [106]. Recommending exercise appears worthwhile and effective in motivated patients offering a veritable option for the management of lean NAFLD patients in whom large weight loss cannot be recommended. To date there are no data on

the effect of exercise alone on histological NASH features ballooning, inflammation and most notably fibrosis.

45) **In normal weight NAFL/NASH patients, increased physical activity to improve insulin resistance and steatosis can be recommended. (Recommendation 31, grade GPP, strong consensus 100%)**

For the small proportion of normal weight NAFL/NASH patients no recommendations can be made on the basis of intervention trials. Since exercise alone has been shown to improve hepatic fat content and insulin resistance in overweight/obese NAFL/NASH patients [103–106] it seems plausible to recommend exercise in normal weight individuals for the improvement of steatosis and insulin resistance. Likewise, a reduction in the consumption of fructose sweetened soft drinks should be considered.

2.2.3.1.2. Diet

46) **Overweight and obese NAFL/NASH patients shall follow a weight reducing diet to reduce the risk of comorbidity and to improve liver enzymes and histology (necroinflammation). (Recommendation 32, grade A, strong consensus 100%)**

In a multi-center randomized study, low-calorie diets were effective and safe in reducing body weight and improving NAFLD within twelve weeks [107]. Likewise, a low-calorie diet was effective in achieving weight loss of at least 5% and improvement of NAFLD [102,108,109]. Data from two trials suggest that the restriction of dietary carbohydrate was more effective than overall caloric restriction in short-term weight loss (two weeks) and in hepatic triglyceride reduction [110,111] while Kirk et al. reported the same decrease in intrahepatic lipid after 11 weeks on either a low or a high carbohydrate diet [112]. Moreover, another trial showed the same beneficial effects regardless of whether the diet was low fat or a low carb [113]. Two trials report beneficial effects of a diet low in saturated fat [114,115]. In a prospective study in obese diabetics comparing isocaloric diets high in animal or plant protein a decrease in intrahepatic fat and insulin resistance was observed after 6 weeks [116]. See also point 48.

47) **In overweight/obese NAFL/NASH patients a 7–10% weight loss shall be aimed for to improve steatosis and liver biochemistry; a weight loss of > 10% shall be aimed for in order to improve fibrosis. (Recommendation 29, grade A, strong consensus 96%)**

Weight loss generally reduces hepatic steatosis, irrespective of how it is achieved [117–119]. Results from the evaluation of paired biopsies in NASH patients achieving weight loss indicate that only substantial weight loss (≥9–10% is accompanied by improvement in fibrosis and even full resolution of NASH [97,101,120–126]. A less pronounced weight loss is associated with improvement in steatosis, inflammation and liver enzymes, but not in fibrosis [100,101,113,127,128]. The potential of bariatric surgery to improve fibrosis of NASH is underscored by two meta-analyses [129,130]. See also points 50 and 51.

48) **In order to achieve weight loss, a hypocaloric diet shall be followed according to current obesity guidelines irrespective of the macronutrient composition. (Recommendation 33, grade A, strong consensus 93%)**

Nutrition counseling of overweight and obese NAFLD patients should be done in accordance with current guidelines for the dietary management of obesity. There is no robust evidence supporting a particular composition of hypocaloric diet unique for use in NAFL/NASH patients. Coffee consumption, however, seems more likely to benefit health than harm, with summary estimates indicating the largest risk reduction for various health outcomes at three to four cups a day. Patients with chronic liver disease seem to benefit most. It has been hypothesized that the rising prevalence of obesity in the last four decades was related to an increased consumption of dietary fructose and high-fructose corn syrup as a sweetener in soft drinks and other foods [131] Increased fructose consumption as well as hepatic fructokinase and fatty acid synthase mRNA have been observed in NAFLD patients when compared to controls [132]. High fructose consumption may increase the risk of NASH and advanced fibrosis, although the association may be confounded by excess calorie intake or by unhealthy lifestyles and sedentary behavior, which are more common in NAFLD [117,133]. The available evidence, however, is not sufficiently robust to draw conclusions regarding NAFLD promoting effects specific to fructose when consumed as ingredient of a normocaloric diet [134,135]. See also point 46.

49) **A Mediterranean diet (MedD) should be advised to improve steatosis and insulin sensitivity. (Recommendation 34, grade B, strong consensus 100%)**

Numerous interventional [136–138] and observational [139,140] studies are available suggesting that a MedD has beneficial effects on body weight, insulin sensitivity and hepatic steatosis and fibrosis, but without clear evidence in respect of preventing the appearance of NAFLD. There is, however, a solid body of clinical evidence supporting the beneficial effect of MedD in terms of lowering the risk of cardiovascular disease and the development of diabetes, conditions that share common etiological factors with NAFLD, like insulin resistance and obesity [141]. Higher adherence to the MedD is not associated with lower likelihood of having NAFLD, but it is associated with less degree of insulin resistance and less severe liver disease among patients with NAFLD [139]. Even without weight loss, MedD reduces liver steatosis and improves insulin sensitivity in an insulin-resistant population with NAFLD, compared to current dietary advice [142].

2.2.3.1.3. Bariatric surgery

50) **In obese NAFL/NASH patients, the efficacy of bariatric surgery regarding weight reduction and improvement in hepatic steatosis and necroinflammation including fibrosis as well as insulin resistance should be considered. (Statement 13, strong consensus 100%)**

The effect of bariatric surgery on liver histology in paired biopsies has been reported in several studies [120–122,124,125,143]. Clearly, the profound weight loss achieved by this approach has the potential to resolve NASH in up to 80–100% and improve fibrosis substantially, the latter being the most relevant outcome regarding patient survival [144]. Also, insulin sensitivity is improved, and a considerable proportion of diabetic patients needs no more antidiabetic treatment.

51) **In otherwise eligible obese NAFL/NASH patients without cirrhosis, after weight reduction diets and intensive lifestyle interventions have failed, bariatric surgery**

should be proposed. (Recommendation 45, grade B, strong consensus 100%)

Lifestyle intervention, although effective in some patients, is often not sufficient to achieve long-term weight loss and resolution of NASH. Currently, no drug treatment has been shown effective, but many compounds are under investigation. Bariatric surgery is a potential treatment option in NAFLD, in particularly its progressive form NASH. There are no systematic randomized controlled trials that evaluated any bariatric surgical procedure to specifically treat NAFLD or NASH. A systematic review and meta-analysis of 15 studies reporting on 766 paired liver biopsies showed that the pooled proportion of patients with improvement or resolution in steatosis was 92%, in steatohepatitis was 81%, in fibrosis was 66% and for complete resolution of NASH was 70% [129]. Perioperative mortality of bariatric surgery is lower in patients without cirrhosis compared to patients with compensated or decompensated cirrhosis (0.3% vs 0.9% and 16.3%) [145]. The joint European guidelines of EASL, EASD and EASO state that in patients unresponsive to lifestyle changes and pharmacotherapy, bariatric surgery is an option for reducing weight and metabolic complications, with stable results in the long-term results [117].

2.2.3.2. Co-Morbidities

52) **In assessing the prognosis of patients in whom NAFL/NASH is an integral component of the metabolic syndrome the effect of non-hepatic comorbidity should be considered. (Statement 9, strong consensus 100%)**

In NAFLD, overall and cardiovascular mortality are increased compared to the general population. NAFLD is associated with an increased standardized mortality ratio compared with the general population and liver disease now ranks after cardiovascular disease and cancer as cause of death. Severe obesity prior to LTx is associated with a higher prevalence of comorbidities (diabetes, hypertension), cryptogenic cirrhosis and increased mortality from infectious complications, cardiovascular disease and cancer [146,147]. Diabetes risk and overt type 2 diabetes are associated with more severe NAFLD, progression to NASH, advanced fibrosis and the development of hepatocellular carcinoma [148,149] independent of serum transaminases. NAFLD patients also have an increased risk (up to 5-fold) of developing type 2 diabetes after adjustment for several lifestyle and metabolic confounders [150]. Therefore, European guidelines recommend that individuals with NAFLD should be screened for diabetes and that patients with type 2 diabetes should be evaluated for the presence of NAFLD irrespective of serum transaminases [117].

53) **NAFL/NASH patients shall be encouraged to abstain from alcohol in order reduce risk for comorbidity and to improve liver biochemistry and histology. (Recommendation 36, grade A, strong consensus 100%)**

Addressing the questions of whether there is a continuous dose–response pattern or a threshold value or an effect of gender or end-points (morbidity vs mortality) of alcohol use Rehm and coworkers analyzed 17 studies in their systematic review and meta-analysis [151]. They conclude that there is a threshold for morbidity from cirrhosis but not for mortality regardless of gender. Once there are any signs of liver disease of any etiology they propose to abstain due to the higher relative risks for any consumption associated with mortality [151]. Furthermore, in NAFL/NASH risks may be aggravated by interaction with drugs taken in association with entities of metabolic syndrome. At variance to the general population, alcohol use may not reduce the risk of cardiovascular disease in patients with NAFLD [152].

54) **Patients with celiac disease and NAFLD/NASH should follow a gluten free diet to improve liver enzymes and histology, and to prevent progression to cirrhosis, in addition to improving intestinal pathology. (Recommendation 37, grade B, strong consensus 96%)**

Celiac disease patients are at increased risk of liver disease prior to or subsequent to the diagnosis of celiac disease. According to a systematic analysis [153] the hazard ratio for NAFL/NASH is 2.8 (95% CI 2.0–3.8) in celiac disease patients with and even higher in the subgroup of children (HR 4.6; 95% CI 2.3-0.1). There are several reports on improvement or even normalization of transaminases with response rates up to 75%–100% upon institution of a gluten free diet [154–158]. A case series from Finland reported on four patients with serious liver disease referred to the transplantation center in whom celiac disease was diagnosed during the evaluation. All patients responded to the gluten free diet and in two diet compliant patient's liver disease resolved completely [159]. Of five US patients with liver cirrhosis and celiac disease ALT, AST and bilirubin improved in the four diet compliant patients; MELD score worsened in one patient with NASH cirrhosis but improved in the remaining three [160]. There is an association between celiac disease and autoimmune liver disease (autoimmune hepatitis, primary biliary cholangitis) and gluten restriction seems to have a role to reduce the risk of complications (malabsorption, osteoporosis, malignancy) in this group of patients.

2.2.3.3. Supplements

55) **Vitamin E (800 IU α-tocopherol daily) should be prescribed to non-diabetic adults with histologically confirmed NASH aiming for improvement of liver enzymes and histology. (Recommendation 38, grade B, strong consensus 100%)**

The efficacy of Vitamin E as an anti-oxidant to ameliorate biochemical and/or histological abnormalities of NASH has been investigated in a number of trials [99,161,162]. There is, however, a great heterogeneity among these trials regarding study power, entry criteria, dosage of vitamin E, formulations of vitamin E used, additional use of other anti-oxidants or other drugs and histologic data to assess outcomes. Despite these limitations, the following conclusions can be drawn regarding adults with NASH: 1. The use of vitamin E is associated with an improvement of liver enzymes (decrease in ALT, AST), 2. Trials evaluating NASH features in paired liver biopsies show improvement in steatosis, inflammation, and ballooning and resolution of steatohepatitis in patients treated with vitamin E when compared to controls, and 3. Vitamin E has limited or no effect on hepatic fibrosis. In the largest RCT (PIVENS trial) the predefined primary endpoint was achieved in a significantly greater number of participants receiving oral vitamin E (800 IU$\cdot d^{-1}$ for two years) compared to placebo (42% vs. 19%, $p < 0.001$, number needed to treat = 4.4) [162]. Re-analysis of the PIVENS trial showed that ALT responses were more frequent in the vitamin E recipients and were associated with the NAFLD Activity Score (NAS), but not fibrosis scores [163]. Interestingly, vitamin E had an added effect on the improvement of ALT, NAS, and fibrosis scores obtained by weight loss $\geq$2.0 kg [163].

56) **Until further data regarding their efficacy are available, antioxidants (e.g. vitamin C, resveratrol, anthocyanin, bayberries) cannot be recommended to treat NAFL/NASH. (Recommendation 39, grade 0, strong consensus 100%)**

Oral resveratrol (3000 mg) for eight weeks had no effect on insulin resistance, steatosis, abdominal fat distribution and plasma lipids or antioxidant activity. ALT and AST levels, however, increased significantly in the resveratrol group [164]. In another trial, 2 × 150 mg resveratrol p. o. for three months was found to improve AST, ALT, LDL and total cholesterol, HOMA-IR and inflammation mediators [165]. One 500 mg capsule of resveratrol together with lifestyle intervention was more effective than lifestyle intervention alone in overweight patients regarding improvement in ALT, inflammatory cytokines and hepatic steatosis [166,167]. Bayberry juice containing high levels of polyphenols had no effect on anthropometric measures and HOMA-IR in Chinese normal weight patients with NAFLD on ultrasound [168]. In a randomized controlled pilot trial, the flavonoid anthocyanin (320 mg p. o. for twelve weeks) decreased ALT and the 2-h loading glucose level [169]. Oral coenzymeQ10 supplementation was reported to reduce waist circumference, serum AST levels and blood total anti-oxidant capacity [170]. In NAFLD patients, a vitamin C intake below the recommended daily allowance has been reported in epidemiological studies, suggesting an association between dietary habits, disease and vitamin C deficiency. The presently available RCTs have not found an effect of vitamin C superior to that of placebo. Thus, the role of vitamin C in NAFLD should be investigated in future adequately controlled RCTs. Abnormally low choline levels have been implicated in the pathogenesis of PN associated liver disease of which some morphological features resemble NAFLD/NASH [171]. A secondary analysis of food questionnaires from 664 participants of three NASH Clinical Research Network trials showed that in postmenopausal women a decreased choline intake was associated with increased fibrosis [172]. Along this line, data suggest that higher dietary choline intake may be associated with a lower risk of NAFLD. On the other hand, a close relation between plasma free choline levels and the grade of liver steatosis and fibrosis has been observed in NASH [173]. There is no data from choline intervention trials. Compared to placebo, oral supplementation of L-carnitine (1 g b.i.d. for 24 weeks) was effective in reducing TNF-α and CRP and in improving liver function, glucose plasma level, lipid profile, HOMA-IR, and histological manifestations of NASH [174]. In diabetic NAFLD patients, oral carnitine-orotate (3 · 824 mg for twelve weeks) was associated with significant improvement in ALT, hepatic steatosis and HbA1c in a double-blind placebo-controlled trial [175]. These are preliminary results and, therefore L-carnitine cannot be recommended yet.

57) **Until further data regarding their efficacy are available, omega-3-fatty acids cannot be recommended to treat NAFL/NASH. (Recommendation 40, grade 0, strong consensus 100%)**

In patients with just NAFLD, there was a trend towards improvement in liver fat in those treated with 4 g of omega-3 fatty acids [176]. However, a multi-center trial comparing two dose regimens of ethyl-eicosapentanoic acid (1.800 mg/d or 2.700 mg/d) with placebo found no effect on liver enzymes, insulin resistance, adiponectin, keratin 18, C-reactive protein, hyaluronic acid and liver histology in 243 patients with biopsy proven NASH [177]. In a smaller controlled trial, 3 g of omega-3 fatty acids improved hepatic fat content but failed to improve NASH by 2 points [178]. In a trial comparing the effect of 4 g of omega-3 fatty acids and dapagliflozin alone or in combination only the combination was more effective than placebo in lowering intrahepatic lipid [179]. The authors of a systematic review and meta-analysis concluded that in NAFLD patients omega-3 fatty acids reduce liver fat, but the optimal dose had not been determined and better controlled trials were needed [180]. In a recent systematic review, however, the authors conclude that marine n-3 PUFAs are likely to be an important tool for NAFLD treatment but further studies are required to confirm this [181]. The authors of another meta-analysis concluded that omega-3 LC-PUFAs are useful in the dietary management of patients with NAFLD but are ineffective on histologic findings in NASH patients [182].

58) **Nutritional supplements containing selected probiotics or synbiotics can be used to improve liver enzymes in NAFL/NASH patients. (Recommendation 41, grade 0, consensus 89%)**

A systematic review identified nine full text papers of randomized clinical trials evaluating probiotics, prebiotics or synbiotics in the treatment of adult NAFLD of which six were excluded due to methodological deficits [183]. A double blind randomized controlled trial in 30 biopsy proven NAFLD patients showed a significant but very modest decrease in ALT, AST, and gGT after three months of treatment with the probiotic but not with placebo [184]. A comparison of probiotics versus standard care showed a decrease of intrahepatic triglycerides (MR spectroscopy) and of serum AST in the ten patients of the probiotic group [185]. In patients with biopsy proven NASH, Bifidobacterium longum with fructo-oligosaccharides and lifestyle modification for 24 weeks, when compared to lifestyle modification alone, reduced AST levels, markers of inflammation, HOMA-IR, serum endotoxin, and NASH histology in both groups but more so in the symbiotic group [186]. In a randomized, double-blind, placebo-controlled clinical trial, 52 patients with NAFLD were randomized to take twice daily for 28 weeks either a synbiotic or a placebo capsule in addition to lifestyle modification. In the synbiotic group, blood levels of ALT, AST, gGT, CRP and inflammatory cytokines decreased to a greater degree than in the placebo group [187]. The daily consumption of 300 g (8 weeks) of a probiotic containing yoghurt was reported to improve liver enzymes in NAFLD patients compared to conventional yoghurt [188].

2.2.3.4. Medical nutrition (EN, PN)

59) **EN or PN shall be administered in NAFL/NASH patients during severe intercurrent illness, when oral nutrition alone is inadequate or impossible or contraindicated. (Recommendation 42, grade GPP, strong consensus 96%)**

There is no data from formal trials of nutrition therapy addressing these questions. An analysis using the database from the Korea National Health and Nutrition Examination Survey found 12% of NAFLD subjects to be sarcopenic and, interestingly, their BMI was significantly higher than that of non-sarcopenic individuals [189]. Also, sarcopenia was consistently associated with significant liver fibrosis. Based on the many reports on the prognostic role of poor food consumption in hospitalized patients in general and patients with ASH or liver cirrhosis in particular experts recommend nutrition support also in NAFLD/NASH patients who cannot achieve an adequate food intake while they are suffering from severe intercurrent illness. Also, in this patient group, malnutrition risk screening and appropriate nutritional assessment are highly encouraged.

60) **In NAFL/NASH patients with a BMI < 30 kg/m^2 EN and/or PN should be done as recommended for ASH patients (Recommendation 43, grade GPP, strong consensus 100%)**

See commentary to point 59 and commentaries to points 33, 34, 38 and 40 on EN/PN in ASH patients.

61) **Obese NAFL/NASH patients with intercurrent illness should be given EN and/or PN with a target energy intake of 25 kcal·kg^{-1} IBW·d^{-1} and an increased target protein intake of 2.0-2.5 g·kg^{-1} IBW·d^{-1}. (Recommendation 44, grade GPP, majority agreement, 71%)**

An increasing number (30–35%) of adult ICU patients are obese and at least 5% are morbidly obese. Nutrition support of such patients is challenging and one of the most difficult aspects in clinical nutrition. Obesity has an impact on the incidence and severity of comorbidities and patient outcome. According to ASPEN guidelines such patients should be cared for according to the basic principles of critical care nutrition aiming for a high protein intake (2.0–2.5 g·kg^{-1} IBW·d^{-1}) for the preservation of lean body mass but a hypocaloric regimen (25 kcal·kg^{-1} IBW·d^{-1}) aiming for the reduction of fat mass and insulin resistance [190]. Among the consensus group, agreement on this recommendation was limited due to the weak evidence available. Facing the increasing number of obese NAFL/NASH patients, however, the reference to the ASPEN critical care guideline was considered appropriate.

2.2.4. Liver cirrhosis (Figs. 10–12)

2.2.4.1. Malnutrition risk

62) **In patients with liver cirrhosis, a high prevalence of malnutrition, protein depletion and trace element deficiency should be anticipated. (Statement 1, strong consensus, 100%)**

In liver cirrhosis, the prevalence and severity of mixed type protein energy malnutrition are related to the clinical stage of chronic liver disease, increasing from 20% in patients with well compensated disease to more than 60% in patients with advanced cirrhosis. Etiology of liver disease per se does not seem to influence the prevalence and degree of malnutrition and protein depletion and the higher prevalence and more profound degree of malnutrition in alcoholics likely result from additional factors including unhealthy life style and socio-economic deprivation. Body composition of cirrhotics is altered profoundly and characterized by protein depletion and accumulation of total body water which may be manifest even in patients with Child-Pugh class A early-stage disease [191–193]. This is paralleled by sodium retention and is thus seldom associated with hyper-natremia. Depletion of potassium, magnesium, phosphate and other intracellular minerals frequently occurs. Deficiency in water soluble vitamins, mainly group B vitamins, is common in cirrhosis, especially that of alcoholic origin. Deficiency in fat soluble vitamins has been observed in cholestasis-related steatorrhea, bile salt deficiency, and in alcoholics. In cirrhosis, malnutrition is associated with a higher prevalence of ascites and hepatorenal syndrome, a greater length of stay and hospital costs [194] as well as higher mortality [193]. In several descriptive studies, higher rates of morbidity [22,195,196] and mortality [23,30,196–198] are reported in patients with preoperative malnutrition and/or sarcopenia who undergo transplantation for end-stage chronic liver disease.

63) **In liver cirrhosis, a stage dependent progressive impairment of carbohydrate, protein and lipid metabolism characterized by hepatic glycogen depletion, impaired non-oxidative glucose metabolism and reduced albumin synthetic rate should be anticipated (Statement 3, strong consensus, 100%)**

In cirrhosis in the post absorptive state, glucose oxidation rate is reduced and hepatic glucose production rate is low despite increased gluconeogenesis due to a depletion of hepatic glycogen [199]. Thus, after an overnight fast metabolic conditions are similar to that in prolonged starvation in healthy individuals [200]. 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. Some 15–37% of patients develop overt diabetes which is associated with an unfavorable prognosis [201,202]. The utilization of oxidative fuels is characterized 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) [200,203]. Plasma levels of essential and polyunsaturated fatty acids are decreased in cirrhosis and this reduction correlates with nutritional status and severity of liver disease [204,205]. In cirrhosis, normal or increased protein turnover due to increased protein breakdown and/or reduced protein synthesis have been observed. Albumin but not fibrinogen synthesis rates correlate with quantitative liver function tests and clinical stages of cirrhosis. Nevertheless, stable cirrhotics are apparently capable of efficient nitrogen retention and significant formation of lean body mass from increased protein intake during oral refeeding [33].

64) **In the management of severely malnourished cirrhosis patients, a poorer survival compared to non-malnourished patients shall be expected. (Statement 8, strong consensus 100%)**

In severely malnourished cirrhosis patients a number of studies reported higher morbidity and mortality [193,206] as well as a higher mortality following LTx [30,195,198,206–209]. Data are controversial regarding a higher prevalence of hepatic encephalopathy in malnourished cirrhosis patients [203,210].

2.2.4.2. Oral nutrition

2.2.4.2.1. Diet counseling

65) **Specific nutritional counselling should be implemented in cirrhotic patients using a multidisciplinary team to improve patients' long-term outcome/survival. (Recommendation 46, grade GPP, strong consensus 100%)**

Nutrition therapy should be included in the management of cirrhosis patients. Specific nutrition counseling has the potential to alter patients' behavior and should include patients' education about the benefit of a healthy diet adapted to the clinical condition and addressing specific concerns. When nutrition prescriptions need to be changed in response to the severity of the disease nutrition counseling can facilitate how to deal with these changes. A small monocentric retrospective study showed a survival benefit when cirrhosis patients received specialized nutrition counseling as compared to no counseling [211]. The authors also reported that counseling involving a multidisciplinary team including physicians, nurses, pharmacists and dieticians was associated with better survival than counseling by just one profession [211].

66) **Multidisciplinary nutrition care should include monitoring of nutritional status and provide guidance for**

achieving nutritional goals. (Recommendation 47, grade GPP, strong consensus 95%)

See commentary to point 65.

67) **Periods of starvation should be kept short by consuming three to five meals a day and a late evening snack should be recommended to improve total body protein status. (Recommendation 58, grade B, strong consensus 100%)**

Based on available published data, patients should have an energy intake of 30–35 kcal·kg^{-1}·d^{-1} and a protein intake of 1.2–1.5 g·kg^{-1}·d^{-1}. In a well conducted prospective trial measuring total body nitrogen the nocturnal administration of ONS has been shown to be more effective in improving total body protein status than daytime ONS [90]. Previously, a late evening carbohydrate snack has been shown to improve protein metabolism in cirrhosis [91,212]. In their systematic review Tsien and coworkers [83] showed that a late evening snack improved nitrogen balance, irrespective of the composition or type of formulation used. They conclude that shortening periods without food by late evening snack is a promising concept to reverse anabolic resistance and sarcopenia of cirrhosis.

68) **Cirrhotic patients in conditions of increased energy expenditure (i. e. acute complications, refractory ascites) or malnutrition, should ingest an increased amount of energy. (Recommendation 50, grade GPP, strong consensus, 100%)**

In general, energy requirements in compensated cirrhosis patients are not higher than in healthy individuals (see points 8 and 10). Moreover, cirrhosis patients have a decreased physical activity level [32] and thus a decreased energy expenditure due to physical activity. Cirrhotic patients during the natural course of the disease tend to spontaneously decrease their dietary intake [84,213]. This is of special relevance in the subgroup (up to 35% of cirrhosis patients) of hyper-metabolic cirrhosis patients [28,29] or in those with advanced cirrhosis with complications when energy expenditure may be increased. Therefore, measurement of energy expenditure is recommended whenever possible (see recommendation 1). Oral nutrition, EN or PN have been utilized in short and long term studies in decompensated and/or malnourished cirrhotic patients with some advantages either in morbidity or in mortality.

69) **In cirrhotic patients, an increased energy intake is not recommended in overweight or obese patients. (Recommendation 51, grade GPP, strong consensus 100%)**

The proportion of overweight or obese cirrhosis patients has increased even in cohorts on the wait list for transplantation [11,214,215]. In chronic liver disease, obesity has been identified as an independent risk factor for a worse clinical outcome [216,217]. Obesity has been proposed to promote portal hypertension. Portal hypertension could be ameliorated by lifestyle intervention for 16 weeks using hypocaloric diet and increased exercise in cirrhosis patients [218]. Therefore, an increased energy intake is not recommended in obese cirrhotic patients.

70) **In obese patients with cirrhosis lifestyle intervention aiming for beneficial effects of weight reduction, which include reduced portal hypertension, should be implemented. (Recommendation 56, grade B, strong consensus 100%).**

In a recent multicenter uncontrolled study [218], the response to hypocaloric normonitrogenous diet and 60 min/wk of supervised physical activity for 16 weeks was evaluated in 50 overweight/obese (BMI ≥26 kg/m^2) patients with compensated cirrhosis. This lifestyle intervention significantly decreased body weight (average, −5.0 4.0 kg). These patients also achieved a significant decrease in portal hypertension as assessed by hepatic venous pressure gradient. No data were reported for other outcomes. If confirmed, these results strongly support lifestyle intervention in obese cirrhotic patients.

2.2.4.2.2. Protein requirement

71) **Non-malnourished patients with compensated cirrhosis should ingest 1.2 g·kg^{-1}·d^{-1} protein. (Recommendation 52, grade B, strong consensus 100%)**

Malnourished and sarcopenic cirrhotic patients experience protein depletion both due to elevated total body protein breakdown and decreased protein synthesis in muscle [191,219]. Increased protein intake is generally well tolerated and safe in cirrhotic patients and ameliorates protein anabolism as shown in previous studies [33,220]. Adequate refeeding was able to induce a significant increase of protein synthesis in a small group of carefully followed malnourished cirrhotic patients [221]. See also point 72.

72) **To replenish malnourished and/or sarcopenic cirrhotic patients the amount of 1.5 g·kg^{-1}·d^{-1} protein should be ingested. (Recommendation 53, grade B – Strong consensus 100%)**

Sarcopenic cirrhotic patients, including those with sarcopenic obesity, may need a higher protein intake in conjunction with exercise to accomplish muscle replenishment. In intervention studies implementing high protein intakes improvement in arm muscle circumference, handgrip strength and albumin was observed [9,222–225]. An improvement in total body protein status was observed, when ONS were consumed nocturnally [90] extending previous observations of a beneficial effect of a late evening carbohydrate or protein snack in cirrhosis patients [91,212,220].

73) **Oral diet of cirrhotic patients with malnutrition and muscle depletion should provide 30–35 kcal·kg^{-1}·d^{-1} and 1.5 g protein·kg^{-1}·d^{-1}. (Recommendation 57, grade B, strong consensus 100%)**

See commentary to point 67.

74) **Protein intake should not be restricted in cirrhotic patients with hepatic encephalopathy as it increases protein catabolism. (Recommendation 54, grade B, strong consensus 100%)**

A very select subgroup of cirrhosis patients, termed protein intolerant, develop encephalopathy on a normal protein intake, but this seems to be a historical phenomenon, as such patients are rarely encountered nowadays. Based on a number of trials it was suggested that protein restriction may not be mandatory for the prevention of hepatic encephalopathy [84,86,221]. As shown in an RCT by Cordoba et al. [226] protein restriction has no advantage on the clinical course of acute hepatic encephalopathy and may increase protein catabolism. After this study the dogma of prescribing protein restriction for cirrhosis patients with hepatic encephalopathy was definitively abandoned, and all efforts were focused on achieving an adequate protein intake in these patients.

2.2.4.2.3. BCAA requirement

75) **In cirrhotic patients who are protein "intolerant", vegetable proteins or BCAA (0.25 g·kg^{-1}·d^{-1}) should be used by oral route to facilitate adequate protein intake. (Recommendation 59, grade B, consensus 89%)**

Excluding trials using BCAA-enriched ONS a meta-analysis found a reduced mortality in a subgroup analysis [227]. After successful treatment of portal hypertension by transjugular intrahepatic stent-shunt (TIPS), cirrhosis patients on normal food (according to ESPEN recommendations) were able to improve their body composition [31,228].

In the very rare case of a "protein intolerant" cirrhosis patient developing encephalopathy when ingesting normal amounts of mixed protein, a vegetable protein diet may be beneficial. Reviews have addressed this issue [229] but there is no data from randomized controlled trials comparing isocaloric and isonitrogenous regimens. One study [230] was uncontrolled and in a more recent study nutritional therapy using a vegetable protein diet was compared to no therapy [231].

76) **Long-term oral BCAA supplements (0.25 g·kg^{-1}·d^{-1}) should be prescribed in patients with advanced cirrhosis in order to improve event-free survival or quality of life (Recommendation 60, grade B, consensus 89%)**

There are no data available from trials comparing a standard enteral formula and an enteral formula enriched in BCAA in cirrhosis patients. BCAA-enriched formulas, however, have been used in trials demonstrating improved survival in severely malnourished ASH and cirrhosis patients [67,68,232,233] or mental state in a highly selected group of protein intolerant cirrhosis patients with encephalopathy [234]. In the two largest trials (174 and 646 patients) oral BCAA supplementation (12 and 24 months) was useful to prevent progressive hepatic failure and to improve surrogate markers and health related quality of life [235,236]. In cirrhosis patients after an episode of HE, BCAA supplementation for twelve months improved minimal hepatic encephalopathy and muscle mass but the recurrence of overt hepatic encephalopathy was not decreased vs the control group [237]. In trials reporting beneficial effects on mental state and/or protein metabolism BCAA were given at doses of 0.20–0.25 g·kg BW^{-1}·d^{-1} [235,236,238,239] or 30 g·d^{-1} [234,237]. In a Cochrane meta-analysis, overall a beneficial effect of BCAA on mental state was found [240] but there are unresolved issues regarding trial methodology [241,242]. In most countries, however, oral BCAA supplements are not reimbursed and the combination of cost and palatability may affect compliance.

2.2.4.2.4. Micronutrients/low sodium diet

77) **In cirrhotic patients, micronutrients should be administered to treat confirmed or clinically suspected deficiency. (Recommendation 55, grade GPP, strong consensus 100%)**

Patients with cirrhosis may present deficiencies in water-soluble vitamins, particularly thiamine, and lipid soluble vitamins such as vitamin D [243,244]. There are no reports which systematically evaluate the requirement of micronutrients in cirrhosis. Like in other conditions, the administration of micronutrients has no proven therapeutic effect apart from the prevention or correction of deficiency states. Zinc and vitamin A supplements by improving dysgeusia may indirectly improve food intake and nutritional state [245,246]. Zinc and selenium deficiency have been observed in patients with alcoholic as well as non-alcoholic liver disease. An impressive association between hepatic encephalopathy and zinc deficiency has been described in case reports [247,248]. Randomized controlled trials, however, showed no therapeutic effect of oral zinc supplementation on hepatic encephalopathy [249–251]. Oral zinc supplementation can increase urea production capacity when previously subnormal plasma levels are normalized [252]. 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 costlier and would delay commencing supplementation. Due to the high prevalence of malnutrition cirrhosis patients are at risk for developing refeeding syndrome and thiamine deficiency.

78) **When prescribing a low sodium (unpalatable) diet the increased risk of even lower food consumption should be balanced against its moderate advantage in the treatment of ascites. Care should be taken to avoid compromising the palatability of the diet after sodium reduction. (Recommendation 61, grade GPP – consensus 78%)**

Based on the pathophysiology of ascites a moderate dietary sodium intake (60 mmol/day) is usually recommended. The potential benefit may be offset by a reduced intake of energy and protein due to poor palatability of such a diet [253,254]. Therefore, great care should be taken to ensure adequate nutrition when prescribing a sodium restricted diet. In ascitic cirrhosis patients with ascites on a low sodium diet, morbidity and mortality rates were lower in patients receiving a balanced diet with BCAA with or without PN support when compared to those recommended a low sodium diet alone [255].

2.2.4.3. Medical nutrition

2.2.4.3.1. EN and PN

79) **In cirrhotic patients, who cannot be fed orally or who do not reach the nutritional target through the oral diet, EN should be performed. (Recommendation 62, grade B, strong consensus 100%)**

There is ample evidence indicating that ensuring a quantitatively adequate nutrient intake should be the primary goal [84,232]. If nutritional requirements cannot be met by oral nutrition alone or in combination with ONS then EN is required. EN has been shown to improve survival and liver function [84,232]. A recent randomized multicenter trial showed no effect on survival or liver function one year after EN using a standard formula for on average 2.8 weeks followed by ONS recommended for two months [256]. The authors, however, do not provide data on ONS treatment adherence. Total energy intake during EN was assessed only in a subgroup and exceeded recommended intake by 28% (3292 ± 781 kcal/d) and raises questions of detrimental effects of overfeeding. In their meta-analysis Ney and co-workers [227] found a mortality reduction in the subgroup analysis of three of the four ONS studies included but not for the whole group of six trials analyzed. Their analysis, however is weakened by the inclusion of one trial aiming for only three days of EN [257] and for the exclusion of two relevant controlled trials [84,232] for no good reasons.

80) **PN should be used in cirrhotic patients in whom oral and/or EN are ineffective or not feasible. (Recommendation 65, grade B, strong consensus 100%)**

The indication for PN in cirrhosis patients who cannot be fed orally or by EN is in keeping with recommendations in non-cirrhotic patients [93]. Care should be taken to avoid infections of the intravenous lines as these patients are more prone to infection and sepsis. Two aspects specific to cirrhosis should be mentioned. In cirrhosis, infused lipids are cleared from plasma and oxidized at rates similar to that in healthy individuals. In infants and children fish oil containing emulsions appear to be associated with a lower risk of cholestasis and liver injury (see points 10,11). At present, there are no clinical outcome data showing a benefit of such emulsions in adult cirrhosis patients. Regarding the composition of amino acid solutions, a standard solution can be used in patients with compensated cirrhosis. Specific "hepatic formula" amino acid solutions aimed at the correction of the plasma amino acid imbalance are complete amino acid solutions high in BCAA (35–45%) but low in tryptophan, aromatic and sulfur-containing amino acids and have been developed for cirrhosis patients with overt hepatic encephalopathy. The efficacy of BCAA or BCAA-enriched solutions has been investigated in controlled but very heterogeneous trials [258,259], the results of which are contradictory. Meta-analyses of these studies showed an improvement in mental state by the BCAA-enriched solutions, but no definite benefit in survival [241,260].

81) **In cirrhotic patients, nutritional intervention (either oral, EN or PN) shall be implemented according to current guidelines for non-cirrhotic patients. (Recommendation 48, grade A, consensus 89%)**

In principle, the differential indications for oral nutrition, EN or PN in cirrhosis patients are not different from those covered in guidelines for non-cirrhotic patients. It should be noted, however, that cirrhosis patients typically exhibit hepatic glycogen depletion and resort to protein catabolism for gluconeogenesis much earlier than non-cirrhotic patients, i.e. as early as after an over-night fast (see chapter 1 general recommendations). Therefore, the timely institution of nutrition is of prime importance to provide metabolic fuel and substrate for protein anabolism.

82) **In cirrhotic patients, nutritional intervention (either oral or EN or PN) should be recommended for potential clinical benefit without an increase in adverse events. (Recommendation 49, grade GPP, strong consensus 100%)**

As commented before, a number of studies on nutrition therapy in cirrhosis patients showed improved clinical outcome including survival. Recent meta-analyses, however, fail to confirm a survival benefit [80–82,227]. Methodologically, these meta-analyses suffer from various flaws like mixing cirrhosis and ASH or including trials with just three days of nutrition or excluding pertinent trials for no obvious reason.

2.2.4.3.2. tubes

83) **Esophageal varices are no absolute contraindication for positioning a nasogastric tube (Recommendation 63, grade 0, strong consensus 100%)**

In ten patients with acute hepatic encephalopathy I-II nasogastric tube feeding using a BCAA-enriched enteral formula was successful with regard to recovery from hepatic encephalopathy without any complication due to variceal bleeding [85]. There is no evidence in the current literature [84,232,257,261] that esophageal varices pose an unacceptable risk to the use of fine bore nasogastric tubes for EN.

84) **PEG placement is associated with a higher risk of complications, due to ascites or varices, and thus, can only be used in exceptional cases. (Recommendation 64, grade 0, strong consensus 100%)**

Regarding the placement of a PEG feeding tube the European guidelines [262] state that serious coagulation disorders (INR > 1.5, PTT > 50 s, platelets < 50,000/mm^3) and severe ascites are contraindications. According to those guidelines no increased morbidity has been observed when a PEG was inserted in the presence of mild to moderate ascites. In a series of 26 cases, however, two deaths occurred as a direct consequence of PEG insertion [263]. It should be kept in mind that in cirrhosis portal hypertension can lead to an increased number of enlarged gastric vessels that may become the source of significant hemorrhage when injured during PEG insertion.

2.2.5. Liver transplantation (LTx) and surgery (Figs. 13 and 14)
2.2.5.1. Preoperative phase
2.2.5.1.1. Screening, assessment and general care

85) **Liver cirrhosis patients scheduled for elective surgery or listed for transplantation should be screened and assessed for malnutrition timely in order to treat malnutrition prior to surgery and thereby improve body protein status. (Recommendation 66, grade B, strong consensus, 100%)**

In malnourished cirrhosis patients, the risk of postoperative morbidity and mortality is increased after abdominal surgery [264,265]. Numerous descriptive studies have shown higher morbidity and mortality in cirrhosis patients with protein malnutrition when such patients undergo LTx [30,198,207–209,266–268]. Recently, sarcopenia and frailty have been shown to carry an increased risk of morbidity and mortality on the waiting list and after transplantation [11,12,14,15,20–23,196,215,233]. Patients on the wait list are at risk due to an inadequately low food intake and those consuming a low protein diet (<0.8 $g \cdot kg^{-1} \cdot d^{-1}$) have an increased wait-list mortality [269]. Data from a pilot study suggest that preoperative nutrition support improves total body protein status and reduces postoperative infection rates [270] but there are no controlled trials showing that preoperative nutritional intervention improves clinical outcome.

86) **In the immediate preoperative period, liver cirrhosis patients should be managed according to the ERAS approach in order to prevent unnecessary starvation. (Recommendation 67, grade GPP, strong consensus 100%)**

Liver glycogen is depleted in cirrhosis patients and therefore it is advisable to take great care to shorten periods without nutrient intake in order to avoid gluconeogenesis from muscle protein in an already protein depleted individual. In liver surgery, too, adoption of ERAS protocols improves morbidity and length of stay when among other measures patients are given carbohydrate containing clear liquid until 2 h preoperatively, early feeding and mobilization [36,271,272].

87) **In liver cirrhosis patients scheduled for elective surgery, nutrition management should proceed as recommended for liver cirrhosis. (Recommendation 68, grade GPP, strong consensus 100%)**

Cirrhotic patients scheduled for surgery should be managed like non-obese patients with cirrhosis using the same targets for energy

and protein intake. Both undernutrition (BMI < 18.5 $kg \cdot m^{-2}$) and severe obesity (BMI > 40 $kg \cdot m^{-2}$) prior to LTx are associated with increased mortality and morbidity [146,147].

2.2.5.1.2. Energy requirement

88) **Preoperatively, a total energy intake of 30-35 $kcal \cdot kg^{-1} \cdot d^{-1}$ (126–147 $kJ \cdot kg^{-1} \cdot d^{-1}$) and a protein intake of 1.2-1.5 $g \cdot kg^{-1} \cdot d^{-1}$ should be aimed for. These ranges cover recommended intakes depending on treatment goals, i.e. maintenance or improvement of nutritional status. (Recommendation 69, grade GPP, strong consensus 100%)**

See commentaries to points 71–73.

89) **Obese patients can be given EN and/or PN with a target energy intake of 25 $kcal \cdot kg^{-1}$ IBW$\cdot d^{-1}$ and an increased target protein intake of 2.0-2.5 $g \cdot kg^{-1}$ IBW $\cdot d^{-1}$. (Recommendation 70, grade GPP, strong consensus 93%)**

Severe obesity prior to LTx is associated with a higher prevalence of comorbidities (diabetes, hypertension), cryptogenic cirrhosis and increased mortality from infectious complications, cardiovascular disease and cancer [146,147]. In this patient group, the presence and extent of ascites seem to increase with the degree of obesity and the subtraction of the amount of ascitic fluid removed can be used to calculate "dry BMI" [146,273]. Some investigators found that severe obesity was associated with increased morbidity and mortality even when patients were classified according to "dry BMI" [146] while others found the amount of ascites and not BMI to increase mortality risk [273] or did not address this issue [147]. Also, in chronic liver disease obesity is an independent risk factor for worse clinical outcome [216,217].

90) **In overweight/obese NASH patients scheduled for elective surgery nutrition management should proceed as recommended for NASH. (Recommendation 71, grade GPP, strong consensus 100%)**

See commentary to point 89.

2.2.5.1.3. BCAA and other specialized regimes

91) **In adults, for preoperative nutrition standard nutrition regimens shall be used, since specialized regimens (e. g. BCAA-enriched, immune-enhancing diets) were not superior to standard regimens regarding morbidity or mortality. (Recommendation 72, grade A, strong consensus 100%)**

Nutritional counselling plus ONS and nutritional counselling alone were equally effective in cirrhosis patients awaiting transplantation [224]. In a controlled randomized trial in cirrhosis patients undergoing transplantation there was no advantage irrespective of whether a special immune-enhancing ONS or a standard ONS was used for preoperative nutrition support [89]. The use of probiotics, however, from listing until transplantation was associated with fewer infections and a more rapid decrease of ALT, AST and lower bilirubin levels postoperatively when compared to controls in a randomized controlled trial [274]. Non-randomized studies by Kaido and colleagues showed fewer postoperative infections in transplanted patients who received preoperative BCAA-enriched ONS [275,276]. A retrospective analysis indicated reduced postoperative bacteremia in LTx recipients receiving oral BCAA supplementation [277].

92) **In children awaiting transplantation, BCAA-enriched formulas should be used in order to improve body cell mass. (Recommendation 73, grade B, strong consensus 93%)**

Pediatric transplant patients with predominantly cholestatic liver disease had improved body cell mass if they received BCAA-enriched formulas [278].

93) **No recommendations can be made regarding donor or organ conditioning by use of specific nutrition regimens, such as i. v. glutamine or arginine, with the object of minimizing ischemia/reperfusion damage. (Recommendation 82, grade GPP, strong consensus 100%)**

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 [279]. The value of donor or organ conditioning which aims to reduce ischemia/reperfusion damage in humans by provision of high doses of arginine or glutamine is currently unknown.

2.2.5.2. Postoperative phase

2.2.5.2.1. Risk of sarcopenia

94) **After LTx for liver cirrhosis, prolonged incomplete recovery of total body nitrogen status should be anticipated. (Statement 5, strong consensus 100%)**

Plank and coworkers reported a loss of 1.0 kg of total body protein (equivalent to 5.0 kg of skeletal muscle) mainly from skeletal muscle immediately after surgery and this loss was not replenished twelve months thereafter [280]. In a study using total body potassium counting with follow-up for 24 months after LTx, an initial postoperative loss but no subsequent gain in body cell mass was observed [281]. As a functional equivalent, Selberg and coworkers [282,283] demonstrated that glucose uptake and non-oxidative glucose disposal by skeletal muscle had not normalized up to twelve months and longer after LTx. Unsurprisingly, respiratory muscle function had not returned to normal up to one year after transplantation [280].

95) **After LTx, the risk of developing sarcopenic obesity and metabolic syndrome should be taken into account and nutritional rehabilitation should aim for an earlier and faster recovery of total body protein and muscle function (Statement 6, strong consensus 100%)**

After transplantation, many patients become obese and develop metabolic syndrome. Studies showed increase in fat mass and a persistence of sarcopenia and impaired glucose disposal by skeletal muscle. These findings show that organ transplantation alone does not normalize the metabolic dysfunction in these patients [284]. Whilst on the transplant wait list, cirrhosis patients suffer from fatigue, a stage dependent loss of quality of life and exercise capacity, and exhibit a very low activity level [214] and a progressive loss of muscle mass. Participants in a structured 12-week exercise protocol had an improvement in 6-min walk distance and quality of life [285]. After transplantation, activity level, quality of life and

exercise capacity in general do not improve to a normal level however, transplant recipients participating in a structured exercise and nutrition protocol had a significantly better gain in VO_2max and quality of life [286].

2.2.5.2.2. General management/energy requirement

96) **After LTx, normal food and/or EN should be initiated within 12-24 h postoperatively to reduce infection rate. (Recommendation 74, grade B, strong consensus 100%)**

EN started as early as 12 h after the operation is associated with a lower rate of infections than no medical nutrition support [287]. In a direct comparison between PN and early EN, both strategies proved to be equally effective with regard to the maintenance of nutritional state [288]. Postoperatively there is a considerable nitrogen loss and patients remain in negative nitrogen balance for a prolonged period [89,280,289] necessitating an increase in the provision of protein or amino acids. Protein or amino acid intakes of 1.2–1.5 $g \cdot kg^{-1} \cdot d^{-1}$ have been reported [289].

97) **After scheduled surgery, chronic liver disease patients should be managed according to the ERAS protocol. (Recommendation 75, grade GPP, strong consensus 100%)**

See commentaries to points 86 and 96.

98) **After the acute postoperative phase an energy intake of 30-35 $kcal \cdot kg^{-1} \cdot d^{-1}$ (126–147 $kJ \cdot kg^{-1} \cdot d^{-1}$) and a protein intake of 1.2-1.5$\cdot g \cdot kg^{-1} \cdot d^{-1}$ should be aimed for. (Recommendation 78, grade GPP, strong consensus 100%)**

See commentaries to points 71–73.

2.2.5.2.3. EN tubes, probiotics, BCAA

99) **For early EN nasogastric/nasojejunal tubes should be used as in non-liver disease surgery. (Recommendation 79, grade B, strong consensus 100%)**

Transplant patients who received early EN 12 h after surgery developed fewer viral infections and had better nitrogen retention than those receiving no medical nutrition support [287]. In comparison with PN, EN reduced complication rates and costs in transplant patients [288]. Whole protein formulas with [290–293] or without pre- and probiotics [287,294,295] or peptide-based formulas have been used for early EN in adult liver transplant recipients. Formulae were administered via nasogastric or nasojejunal tubes [287,288,292,294] or via catheter jejunostomy [290] placed during laparotomy.

100) **After transplantation, enteral formula together with selected probiotics should be used to reduce infection rate. (Recommendation 80, grade B, consensus 86%)**

Perioperative administration of pre-and probiotics (Lactobacillus spp. and other lactic acid metabolizing bacteria) compared to prebiotics was associated with a reduction in infectious complications [292]. A recent meta-analysis [296] which included that study and two further randomized trials using a single Lactobacillus sp [291]. and two Lactobacillus spp. plus Bifidobacterium sp [290]. showed reduced infection rate with pre-and probiotics.

101) **BCAA-enriched formulas can be used in patients with hepatic encephalopathy in need of EN. (Recommendation 81, grade 0, majority agreement 79%)**

A recent meta-analysis [240] also showed that oral/enteral BCAA compared with isonitrogenous controls are beneficial for hepatic encephalopathy in cirrhosis. To date, the question of whether BCAA-enriched formulas or other special components of the nutrition solution can prevent sarcopenic obesity in long-term survivors of LTx has not been addressed in studies.

2.2.5.2.4. PN indications

102) **PN should be preferred to no feeding in order to reduce complication rates and length of mechanical ventilation and length of stay in ICU, when oral nutrition or EN is impossible or not practicable. (Recommendation 76, grade B, consensus 86%)**

After transplantation, postoperative PN is superior to the infusion of fluid and electrolytes in reducing time on the ventilator and length of stay in ICU [297]. After non-transplant abdominal surgery cirrhosis patients have a reduced rate of complications and improved nitrogen economy if they receive nutritional support instead of just fluid and electrolytes [298,299]. EN (via jejunostomy) was associated with improved 7-day nitrogen balance compared with sequential PN/EN [299].

103) **PN should be used in patients with unprotected airways and hepatic encephalopathy when cough and swallow reflexes are compromised or EN is contraindicated or impracticable. (Recommendation 77, grade GPP, strong consensus 100%)**

See commentary to point 39.

Conflict of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict of interest forms are stored at the ESPEN guideline office and can be reviewed by ESPEN members with legitimate interest upon request to the ESPEN executive.

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