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ESPEN guideline on clinical nutrition in liver disease

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SUMMARY

This update of evidence-based guidelines (GL) aims to translate current evidence and expert opinion into recommendations for multidisciplinary teams responsible for the optimal nutritional and metabolic management of adult patients with liver disease. The GL was commissioned and financially supported by ESPEN. Members of the guideline group were selected by ESPEN.

We searched for meta-analyses, systematic reviews and single clinical trials based on clinical questions according to the PICO format. The evidence was evaluated and used to develop clinical recommendations implementing the SIGN method.

A total of 85 recommendations were made for the nutritional and metabolic management of patients with acute liver failure, severe alcoholic steatohepatitis, non-alcoholic fatty liver disease, liver cirrhosis, liver surgery and transplantation as well as nutrition associated liver injury distinct from fatty liver disease. The recommendations are preceded by statements covering current knowledge of the underlying pathophysiology and pathobiochemistry as well as pertinent methods for the assessment of nutritional status and body composition.

1. Introduction

The prognostic and therapeutic role of nutritional issues in the management of patients with liver disease has been known for long [1] and therefore, nutritional status was one of the variables in the original prognostic score devised by Child and Turcotte [2]. Since publication of the first ESPEN guidelines (GL) on nutrition in liver disease [3] and the subsequent updates [4,5] a considerable body of new evidence has accumulated necessitating an update of the GL. In the past twenty years new methods for the assessment of nutritional status and the recognition of the prognostic role of sarcopenia are just two among many other major achievements which are covered in the updated ESPEN GL that is based on the current ESPEN guideline methodology [6]. In recognition of the increasing disease burden from non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) the current GL hold a new chapter addressing the nutritional management of NAFL/NASH patients. Furthermore, a second new chapter addresses clinical questions arising from nutrition associated liver injury (NALI) distinct from NAFL/NASH. In the current guidelines' working group experts from three global regions (Europe, America, Australasia) could base their work on the current GL of the German Society for Nutritional Medicine [7] implementing the identical methodology. The aim of the current GL is to translate current evidence and expert opinion into recommendations for multidisciplinary teams responsible for the optimal metabolic management of patients with liver disease.

1.1. Target population

This GL is aimed to address clinically relevant issues in the nutritional and metabolic management of adult patients with liver disease.

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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
GL	guideline
HCC	hepatocellular carcinoma
HE	hepatic encephalopathy
ICU	intensive care unit
IFALD	intestinal failure associated liver disease
LC	liver cirrhosis
LT	liver transplantation
MCT	medium-chain triglyceride
MEDD	Mediterranean diet
MRT	magnetic resonance tomography
NAFL	non-alcoholic fatty liver
NAFLD	non-alcoholic fatty liver disease
NALI	nutrition associated liver injury
NASH	non-alcoholic steatohepatitis
OLT	orthotopic liver transplant
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
RFH-NPT	Royal Free Hospital Nutrition Prioritizing Tool
RFH-SGA	Royal Free Hospital SGA
SGA	subjective global assessment
SMOF	soy-bean based lipid and olive oil and MCT-lipid and fish oil
UDCA	ursodeoxycholic acid
VA study	Veteran Affairs study

1.2. Target users

This GL is intended to be used by 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

2.1. General methodology

This guideline was developed in accordance with the standard operating procedure for ESPEN guidelines and consensus papers [6]. It is based in part on the German guideline "Clinical Nutrition in the Gastroenterology (Part 1) – Liver" [7], which was updated and extended by an international expert group consisting of five physicians (MP, WB, SD, MM, SCB), one physicist (LP) and one nutrition scientist (TS).

Based on the standard operating procedures for ESPEN guidelines and consensus papers, the first development step of this guideline was the formulation of so-called PICO questions to address specific **p**atient groups or **p**roblems, **i**nterventions, **c**ompare different therapies and be **o**utcome-related [6]. Originally, 59 PICO were created and split into seven main chapters "General", "Acute Liver Failure", "Alcoholic Steatohepatitis", "Non-alcoholic Steatohepatitis", "Cirrhosis", "Transplantation and Surgery" and "Nutrition Associated Liver Injury". To answer these PICO questions, a literature search was performed to identify suitable meta-analyses, systematic reviews and primary studies (for details see below, "search strategy"). The PICO questions were allocated to subgroups/experts for further working. The group met 2016 in Ljubljana, Slovenia, for one meeting on November 24 and 25, on occasion of the EASL Monothematic Conference Nutrition in Liver Disease on November 25 and 26, 2016. Finally, 106 recommendations and statements were created. To grade the literature, the grading system of the Scottish Intercollegiate Guidelines Network (SIGN) [8] was used. The allocation of studies to the different levels of evidence is shown in Table 1. The working group added commentaries to the recommendations to explain and support the basis of the recommendations.

The grades of recommendation were decided according to the levels of evidence assigned (Table 2). In some cases, a downgrading from the recommendation grades generated based on the levels of evidence according to Tables 1 and 2 was necessary, e. g. due to the lack of quality of primary studies included into a meta-analysis. Such cases are described in the commentaries accompanying the respective recommendations. The wording of the recommendations reflects the grades of recommendations: Level A is indicated by "shall", level B by "should" and level 0 by "can/may". The good practice points (GPP) are based on experts' opinions due to the lack of studies. For the GPP recommendations, the wording can be chosen deliberately.

If applicable, the recommendations were assigned to the outcome models according to Koller et al., 2013 [9], see Table 3.

Between 17th February and 23rd March 2017, an online voting on the recommendations was performed using the guideline-services.com platform. Members of ESPEN guideline projects and of the ESPEN council (country representatives) were invited to vote and to provide comments. 64 recommendations reached an agreement >90%, 40 recommendations reached an agreement of >75–90% and three recommendation an agreement ≤75%. Recommendations with strong consensus (indicated by an agreement higher than 90%, see Table 4) were directly passed. All others were voted on again during a consensus conference which took place on 24th April 2017 in Frankfurt/Main, Germany. During this consensus conference, 17 recommendations were changed into statements. 22 of the recommendations/statements achieved an agreement of >90%, 13 an agreement of >75–90% and two an agreement of >50–75%. Six recommendations were rejected due to low agreement or by decision of the group and two additional recommendations were voted on. In total, the guidelines now comprise 85 recommendations and 17 statements. In support of the recommendations and the assigned grade of recommendations, the ESPEN guideline office created evidence tables of relevant meta-analyses, systematic reviews and (R)CTs. These evidence tables are available online as Supplemental Materials to this guideline.

2.2. Search strategy

The updated German S3-Guideline on Nutrition in Liver Disease [7] was produced according to almost the same rules as the current ESPEN guidelines, and therefore, the Guideline Editorial Office decided to use them as a base for the updated ESPEN guidelines. Accordingly, a new comprehensive literature search was performed for the period 01-08-2011 through 22-11-2016 extending the

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Table 1
Definition of levels of evidence.

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

According to the Scottish Intercollegiate Guidelines Network (SIGN) grading system.
Source: SIGN 50: A guideline developer's handbook. Quick reference guide October 2014 [8].

Table 2
Definition of grades of recommendation [6].

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; orA body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; orA body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; orand demonstrating overall consistency of results; orExtrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; orExtrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

Table 3
Outcome models used in clinical studies.

Endpoints with implications for evaluating trials in clinical nutrition	Examples
Biomedical endpoint (BM)	e.g. improvement of body weight, body composition, morbidity, mortality
Patient-centered/-reported endpoint (PC)	e.g. validated quality-of-life score
Health economic endpoint (HE)	e.g. QALYs or budget savings
Decision-making endpoint (DM)	e.g. clinical parameters or biomarkers that allow to make a clinically relevant decision such as transfer from ICU to a normal ward or nutritional support yes/no
Integration of classical and patient-reported endpoint (IE)	The combination of BM and PC, e.g. complex scores such as the Frailty Index

Adapted from Koller et al. [9].

Table 4
Classification of the strength of consensus.

Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75−90% of the participants
Majority agreement	Agreement of >50−75% of the participants
No consensus	Agreement of <50% of the participants

According to the AWMF methodology [10].

literature search of the German guideline which covered the period 01-01-2006 until 31-07-2011. The search was done for systematic reviews and (randomized) controlled clinical trials with the keywords and filters presented in Table 5. After removal of duplicates and abstracts, 830 articles remained from originally 957 hits and were assigned to topics [1] acute liver failure [2], alcoholic steatohepatitis [3], non-alcoholic steatohepatitis [4], liver cirrhosis [5], transplantation & surgery, or [6] nutrition associated liver disease.

Titles and abstracts were screened using the following predefined inclusion/exclusion criteria:

- paper is written in English
- paper is a controlled trial or a systematic review
- paper is a meta-analysis

Table 5
Criteria for systematic search for literature − databases, filters and keywords.

Publication date	From 01 − 08-2011 to 22-11-2016
Language	English
Databases	Pubmed
Filters	human
Publication type	controlled trial, systematic review
Keywords	(liver disease) AND nutrition

After the screening described above, 122 relevant articles were detected. Additional references from studies cited in guidelines, SLRs or (R)CTs were also included, if they did not appear in the original list. After 18 months 49 relevant new articles were retrieved. Articles were allocated to PICO questions by the group member in charge of the appropriate chapter: acute liver failure (WB), alcoholic steatohepatitis (SD), non-alcoholic steatohepatitis (MP, TS), liver cirrhosis (MM), transplantation and surgery (LP), nutrition associated liver disease (MP).

3. General

3.1. In adults, what is the effect of liver disease on a. nutritional status, b. energy metabolism, c. substrate metabolism?

Statement 1

In patients with cirrhosis, a high prevalence of malnutrition, protein depletion and trace element deficiency should be anticipated. (BM)
Strong consensus (100% agreement)

Commentary

In liver cirrhosis (LC), 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 [11–13].

Etiology of liver disease per se does not seem to influence the prevalence and degree of malnutrition and protein depletion [11,13,14] 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 [14–16]. 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 [17,18]. Deficiency in fat soluble vitamins has been observed in cholestasis-related steatorrhea, bile salt deficiency, and in alcoholics [19,20].

In LC, malnutrition is associated with a higher prevalence of ascites and hepatorenal syndrome, a greater length of stay and hospital costs [21] as well as higher mortality [16,21–23]. In several descriptive studies, higher rates of morbidity [24–29] and mortality [27,29–34] are reported in patients with preoperative malnutrition and/or sarcopenia who undergo transplantation for end-stage chronic liver disease.

Statement 2

In acute liver failure (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. (BM)

Strong consensus (100% agreement)

Commentary

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 [35–37]. In ALF, the splanchnic organs do not take up amino acids whereas in healthy humans and those with severe sepsis there is splanchnic bed uptake [35]. 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) hyperinsulinemia due to increased secretion and reduced degradation [38–40]. In ALF, the splanchnic tissues show alteration from net glucose release to net glucose uptake [35]. 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 [40]. 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 [41].

Statement 3

In LC, 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 (BM).

Strong consensus (100% agreement)

Commentary

In LC 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 [42]. Thus, after an overnight fast metabolic conditions are similar to that in prolonged starvation in healthy individuals [43]. 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 [44,45]. The extent to which glucose deposition as glycogen is impaired just in skeletal muscle or in both muscle and liver is not known [46,47]. Some 15–37% of patients develop overt diabetes which is associated with an unfavorable prognosis [48,49].

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) [33,43,50–52]. After a meal, the suppression of lipid oxidation is not uniformly impaired [53,54]. Plasma clearance and lipid oxidation rates are not reduced and thus, the net capacity to utilize exogenous fat does not seem to be impaired [55,56]. Plasma levels of essential and polyunsaturated fatty acids are decreased in cirrhosis and this reduction correlates with nutritional status and severity of liver disease [57,58].

In overweight or obese patients with NAFLD both hepatic and whole-body fat oxidation rates were found reduced under basal conditions and following exercise compared to lean controls (NAFLD 34.1 kg/m^2; controls 23.4 kg/m^2) [59]. The ability to oxidize fat in basal conditions was inversely related to histological findings including severity of steatosis and disease activity.

In LC, normal or increased protein turnover due to increased protein breakdown and/or reduced protein synthesis have been observed [60]. Non-abstinent LC patients have higher leucine flux and non-oxidative disposal than abstinent LC patients or controls indicating a catabolic effect of alcohol [61]. Albumin but not fibrinogen synthesis rates correlate with quantitative liver function tests and clinical stages of cirrhosis [62,63]. Nevertheless, stable cirrhotics are apparently capable of efficient nitrogen retention and significant formation of lean body mass from increased protein intake during oral refeeding [64].

Statement 4

In ALF, alcoholic hepatitis (ASH) and cirrhosis, resting energy expenditure (REE) is usually increased; patients with nonalcoholic fatty liver disease (NAFLD) have a normal REE (BM).

Consensus (90% agreement)

Commentary

In ALF patients, measurement of energy expenditure is not performed as a standard procedure [65]. However, studies using indirect calorimetry showed an increase in REE by 18% or 30%, respectively, in comparison with healthy controls [66,67]. 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 [68,69] or

patients with LC [70]. However, when related to their reduced muscle mass REE in ASH patients was up to 55% higher than that in healthy controls [68,69]. In alcoholics without biochemical evidence of liver disease but not in patients with alcoholic LC an increased REE (25.8 vs 20.8 kcal $\times$ kg^{-1} $\times$ d^{-1}) was observed [71]. Likewise, in alcoholics with fatty liver, ASH or LC excessive alcohol consumption was associated with increased REE (26%); a decrease in REE consistently occurred four days after abstinence from alcohol [72]. After adjustment for body mass, REE was higher by 11% in alcoholics with or without liver disease compared to healthy social drinkers [73].

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. In severely obese men with NAFLD and metabolic syndrome, REE was higher by 17% than in those without metabolic syndrome [74]. Comparing individuals with less difference in BMI (NAFLD 27.7 kg/m^2; controls 25.3 kg/m^2) Kotronen et al. [75] found no difference in REE (77.4 $\pm$ 1.4 vs 75.6 $\pm$ 1.0 J/kg FFM/min) after adjustment for fat-free mass [75].

Measurement of REE in LC and in controls showed no difference when REE was related to body surface area [43,53,66,71] or body mass (LC: 22–27 kcal $\times$ kg^{-1} $\times$ d^{-1}) [52,53,61,76]. REE showed increased values in LC when REE was related to lean body mass in terms of urinary creatinine excretion [53,66,77] or in terms of body cell mass [53].

3.2. In adults with liver disease, what is the energy requirement in a. ALF, b. ASH, c. NASH, d. LC?

Recommendation 1

Due to considerable inter-individual variability, REE should be measured using indirect calorimetry, if available. (BM)
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

Whenever available, indirect calorimetry should be used to measure REE, since in an individual patient measured REE may differ considerably from estimated values [78]. Measured REE is higher than predicted in up to 35% of cirrhotic patients (hyper-metabolism), and below the predicted value in 18% of the patients [33,79,80]. In LC hyper-metabolism was associated with reduced event-free survival and unfavorable outcome after transplantation [31,79] and seems to regress with improvement of body composition [81]. As a less expensive, valid and rapid method hand-held calorimetry has been proposed [82]. 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 [83].

Recommendation 2

Patients with chronic liver disease and a sedentary lifestyle should receive a total energy supply of 1.3 x REE. (BM)
Grade of recommendation B – Consensus (81% agreement)

Commentary

Estimates of total energy expenditure (32 kcal $\times$ kg^{-1} $\times$ d^{-1}) indicate that the 24 h energy requirement of LC patients amounts to about 1.3 $\times$ measured REE (24 kcal $\times$ kg^{-1} $\times$ d^{-1}) [64,84]. Diet-induced thermogenesis [54,85] and the energy cost of defined physical activity in stable cirrhosis patients [85–87] also show no deviation from values obtained in healthy individuals. However, the level of spontaneous physical activity is considerably lower in patients with LC. It is likely that the increased energy requirement in advanced illness is balanced by diminished physical activity reflecting the poor physical condition [87,88].

In cirrhotics without ascites, 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 LC of whom only four were completely evaluated [89] 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 [90]. In general, non-protein energy provision of 1.3 $\times$ REE is sufficient [91,92]. In a longitudinal study, postoperative hyper-metabolism peaked on day 10 after the transplantation at 124% of the predicted basal metabolic rate [93]. By six to twelve months after transplantation there was no longer a difference between the measured and predicted basal metabolic rate [76,93].

3.3. In adults with liver disease, what is the effect of liver transplantation (LT) on a. nutritional status, b. energy metabolism, c. substrate metabolism?

Statement 5

After LT for LC, prolonged incomplete recovery of total body nitrogen status should be anticipated. (BM)
Strong consensus (100% agreement)

Commentary

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 [93]. In a study using total body potassium counting with follow-up for 24 months after LT, an initial postoperative loss but no subsequent gain in body cell mass was observed [94]. As a functional equivalent, Selberg and coworkers [45,95] demonstrated that glucose uptake and non-oxidative glucose disposal by skeletal muscle had not normalized up to twelve months and longer after LT. Unsurprisingly, respiratory muscle function had not returned to normal up to one year after transplantation [93].

Statement 6

After LT, 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 (BM).
Strong consensus (100% agreement)

Commentary

After transplantation, many patients become obese and develop metabolic syndrome [96]. Body composition analyses 50 and 93 months after liver or kidney transplantation respectively, show that despite good graft function, there is a disproportionate increase in

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fat mass and a persistence of sarcopenia [93,97,98] and impaired glucose disposal by skeletal muscle [45,95]. These findings show that organ transplantation alone does not normalize the metabolic dysfunction in these patients [98]. Whilst on the transplant wait list LC patients suffer from fatigue [99], a stage dependent loss of quality of life and exercise capacity [100], and exhibit a very low activity level [101] and a progressive loss of muscle mass (see recommendation 5). Participants in a structured 12-week exercise protocol had an improvement in 6-min walk distance and quality of life [102]. After transplantation, activity level, quality of life and exercise capacity in general do not improve to a normal level [99,103,104]. However, transplant recipients participating in a structured exercise and nutrition protocol had a significantly better gain in VO_2max and quality of life [105].

3.4. In adults with liver disease what is the effect of nutritional status on the prognosis of a. ALF, b. alcoholic steatohepatitis, c. NASH, d. LC, e. transplantation & surgery?

Statement 7

In ALF patients, obesity is associated with an increased risk of death or need for transplantation and an increased mortality after transplantation. (BM)
Strong consensus (96% agreement)

Commentary

In ALF, there is only very limited data available regarding the effect of nutritional status on its course and prognosis. Rutherford and colleagues [106] analyzed 782 adult ALF patients prospectively enrolled from 1998 to 2004. They found the same prevalence of obesity (30%) in ALF patients as in the general population and between BMI categories the proportion of patients being listed for transplantation was not different. 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 higher risk of dying after transplantation. In a small retrospective series, overweight patients were found more susceptible to ALF [107]. In severely undernourished anorexia nervosa patients an ALF-like condition has been described [108] without morphologic evidence of hepatocyte necrosis [109]. Patients recovered completely upon adequate refeeding.

Statement 8

In the management of severely malnourished ASH and cirrhosis patients, a poorer survival compared to non-malnourished patients shall be expected. (BM)
Strong consensus (100% agreement)

Commentary

Undernourished ASH patients had a higher rate of morbidity and mortality in the reports of the combined data from the American Veteran Affairs (VA) study [110–112]. The VA study data show a clear association between low intake of normal food and high mortality [110] and this finding has been confirmed recently [113].

In severely malnourished LC patients a number of studies reported higher morbidity and mortality [16,22,114,115] as well as a higher mortality following LT [22,25–28,31,33,114–116]. Data are controversial regarding a higher prevalence of hepatic encephalopathy (HE) in malnourished LC patients [50,117,118].

Statement 9

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. (BM)
Strong consensus (100% agreement)

Commentary

NAFLD is defined by the presence of hepatic steatosis when causes for secondary fat accumulation in the liver such as alcohol consumption, HCV infection, drug-induced or hereditary liver disease have been excluded [44,119,120]. NAFLD is histologically further categorized into NAFL characterized by steatosis alone without hepatocellular injury and NASH which is characterized by the combination of steatosis and inflammation and hepatocyte injury that may progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [44,119,120]. The definition of significant alcohol consumption has been inconsistent and ranges from 10 to 40 $g \times d^{-1}$ have been reported [44,119,120].

In NAFLD, overall and cardiovascular mortality are increased compared to the general population [121–123]. NAFLD is associated with an increased standardized mortality ratio compared with the general population [124] and liver disease now ranks after cardiovascular disease and cancer as cause of death. Severe obesity prior to LT is associated with a higher prevalence of comorbidities (diabetes, hypertension), cryptogenic cirrhosis and increased mortality from infectious complications, cardiovascular disease and cancer [125,126].

Diabetes risk and overt type 2 diabetes are associated with more severe NAFLD, progression to NASH, advanced fibrosis and the development of HCC [127,128] independent of serum transaminases [129]. NAFLD patients also have an increased risk (up to 5-fold) of developing type 2 diabetes after adjustment for several lifestyle and metabolic confounders [130]. 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 [119].

3.5. In adults with liver disease, which methods should be used to a. identify patients at nutritional risk and b. assess nutritional status?

Recommendation 3

Liver disease patients should be screened for malnutrition using a validated tool.
Grade of recommendation B – Strong consensus (93% agreement)

Commentary

NRS-2002 and MUST are validated tools to screen hospitalized patients for risk of malnutrition [131,132] and are recommended by ESPEN [133]. The Royal Free Hospital Nutrition Prioritizing Tool (RFH-NPT) has been developed as a screening tool for malnutrition in liver disease patients [134,135]. In a head-to-head comparison, the RFH-NPT was more sensitive than the NRS-2002 to identify liver patients at risk for malnutrition [136]. NRS-2002 was considered helpful in identifying malnourished LC patients with

HCC [137]. According to a recent review, none of the available screening tools has been validated rigorously in LC patients leaving RFH-NPT as the best option currently available [138].

Statement 10

Phase angle (measured by bioelectrical impedance analysis) or handgrip strength allow assessment of mortality risk. (BM)
Strong consensus (93% agreement)

Commentary

The accurate quantitative measurement of nutritional status is difficult in chronic liver disease patients with fluid overload [139,140] and/or impaired hepatic protein synthesis (e.g. albumin) [62,63]. Sophisticated methods are required such as total body potassium count [16,141] or in vivo neutron activation analysis [14,15] or isotope dilution [139].

For the nutritional assessment of ASH patients in the VA trials a composite scoring system was used [110–112]. This scoring system has been modified repeatedly; one of the later publications of this series also reported the prognostic significance of the absolute CD8+ count and hand grip strength [142]. The authors observed a close association between low food intake and high mortality [110].

In LC, nutritional status can be assessed using bedside methods, such as the Subjective Global Assessment (SGA) [116,139,143] or the modified Royal-Free-Hospital SGA (RFH-SGA) combining SGA and anthropometry [144]. The RFH-SGA is a strong predictor of morbidity and mortality, but it is time consuming and requires a trained dietician [29,144,145]. Anthropometry of midarm circumference and triceps skinfold thickness are non-invasive bed-side methods [114,115] but suffer from high inter-observer variability.

Handgrip strength is lower in protein depleted LC patients [14,146] and is a good predictor of the rate of complications within the next year [28,147,148] but is an insensitive measure of fatigue [149]. Handgrip strength is better preserved in LC of viral as opposed to alcoholic or cholestatic etiology [14]. Handgrip strength appears a valuable tool to measure efficacy of nutritional intervention [150].

In LC patients, 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 [23,141,151,152]. In LC, low phase angle is associated with increased mortality as in many other disease entities [23,143,153,154].

Recommendation 4

In NASH, cirrhosis and LT, the presence or absence of sarcopenia should be assessed since sarcopenia is a strong predictor of mortality and morbidity. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 5

Radiologic methods (DXA or when CT/MRT images are available for other reasons) should be used to diagnose sarcopenia. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary to recommendations 4 and 5

Sarcopenia is the key feature of malnutrition in LC 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 [155]. On CT images at the level of lumbar vertebra 3 [156] or lumbar vertebra 4 [157] skeletal muscle area can be measured and normalized for stature [158]. The skeletal muscle area at L3 has been shown to be linearly correlated with whole body muscle mass [158]. Loss of skeletal muscle mass on CT has been associated with increased mortality in LC patients [156,159,160], obese LC patients [161], LC patients wait listed for transplantation [162] and in orthotopic liver transplant (OLT) recipients [24,34,163]. After TIPS, failure to reverse sarcopenia was associated with worse survival [157] and after transplantation, new-onset sarcopenia was associated with a trend for higher mortality [164]. In NASH patients a progressive loss of muscle mass has been observed [165].

A French group showed that transverse psoas muscle thickness measured at the level of the umbilicus was inversely correlated with death on the wait list [162]. Low psoas muscle area at lumbar vertebra 3 level was associated with increased mortality and morbidity [29]. A systematic comparison of the analysis of psoas muscle alone vs total skeletal muscle area at L3 level has raised concerns about use of the psoas muscle alone to define sarcopenia or measure muscle loss [166,167].

In order to obviate costly and invasive radiologic imaging ultrasound-based protocols for the assessment of muscle mass have been proposed [168] and await further validation.

In LC 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 CT derived skeletal muscle index was associated with increased mortality [169,170]. In LC 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 [171] or death on the wait list or delisting [172,173].

In LC patients, there is a profound reduction in exercise capacity and this reduction is only moderately ameliorated after transplantation as reviewed in detail by Williams & McKenna [104]. LC patients with a VO_2max <60% of normal had a 50% one-year survival when transplanted [30,32]. Actively exercising transplant recipients, however, can restore their VO_2max to normal [174].

4. Acute liver failure

4.1. Preliminary remarks

ALF typically affects young adults and develops in the absence of pre-existing chronic liver disease. Its rapidity of development is such that most patients will not have evidence of malnutrition at time of illness onset, though nutritional compromise may develop during the period of acute illness severity, resolution and recovery. Its rarity, severity and rapid trajectory is such that few clinical trials of any sort – including those of nutritional interventions – have occurred. Therapeutic interventions are thus mainly based upon clinical observation in patients with ALF, and extrapolation from other critical illness. Despite this lack of an evidence base, outcome for patients with ALF has improved markedly over recent years suggesting that the approaches adopted do have clinical merit 175].

Two European surveys of nutritional practice have been published and suggest a general commonality of approach, though detail may vary [65,176]. Measures to stabilize metabolism and vital functions, support hepatic regeneration and prevent or treat brain edema are taken as of central importance. Nutritional therapy has three principal objectives:

- Ensuring the adequate provision of energy, by giving glucose, lipid, vitamins and trace elements.
- Ensuring optimal rates of protein synthesis by providing an adequate intake of protein or amino acids, respectively.
- Avoiding metabolic complications of nutritional therapy though ensuring euglycemia and prevention of hyper-ammonemia and hyper-triglyceridemia.

4.2. In ALF patients, when is nutritional therapy indicated/ contraindicated to support recovery from ALF?

Recommendation 6

In malnourished ALF patients enteral nutrition (EN) and/or parenteral nutrition (PN) should be initiated promptly, as in other critically ill patients.
Grade of Recommendation GPP – Strong consensus (96% agreement)

Recommendation 7

ALF patients without malnutrition should be provided with nutritional support (preferentially EN) when they are considered unlikely to resume normal oral nutrition within the next five to seven days, as in other critical Illness.
Grade of Recommendation GPP – Strong consensus (96% agreement)

Recommendation 8

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 hyper-ammonemia is controlled. When protein administration is commenced, arterial ammonia should be monitored to ensure no pathological elevation occurs. (BM)
Grade of Recommendation GPP – Consensus (90% agreement)

Commentary to recommendations 6–8

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 intensive care unit (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 (HE) 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 HE 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.

There are no data on the optimal methods to assess nutritional status in patients with ALF. It seems likely that as in critical illness, cirrhosis or acute alcoholic steatohepatitis, simple bedside tools such as SGA or anthropometry are adequate for identifying patients with malnutrition [5].

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 [177,178]. 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.

4.3. In ALF patients, which are the conditions to safely use oral nutrition to achieve adequate nutrient supply?

Recommendation 9

Patients suffering from only mild HE can be fed orally as long as cough and swallow reflexes are intact.
Grade of Recommendation GPP – Strong consensus (100% agreement)

Recommendation 10

In patients with mild HE oral nutritional supplements (ONS) should be used when feeding goals cannot be attained by oral nutrition alone.
Grade of Recommendation GPP – Consensus (85% agreement)

Commentary to recommendations 9 and 10

There are no data from controlled clinical trials in ALF to inform these recommendations. They are based on clinical practice to use normal physiologic modes of feeding as long as they are functional and to resort to EN and/or PN only as second- or third-line options. Close monitoring of oral intake is required to ensure that patients are able to maintain adequate volitional intake. In all sub-types of ALF risk of HE progression with loss of airway control and aspiration exists, and close clinical monitoring of HE level is required.

4.4. In ALF patients who cannot be fed orally, what is the evidence to prefer EN over PN to achieve better survival and/or less complications?

Statement 11

Current clinical practice adopted in many European liver units demonstrates the safety and feasibility of EN in ALF patients.
Strong consensus (100% agreement)

Recommendation 11

ALF patients who cannot be fed orally should receive EN via nasogastric/naso-jejunal tube.
Grade of Recommendation GPP – Strong consensus (100% agreement)

Recommendation 12

EN should be performed by starting with low doses independent of the grade of HE.
Grade of Recommendation GPP – Consensus (80% agreement)

Commentary to statement 11, recommendations 11 and 12

According to ESICM guidelines [179] 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.

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Recommendation 13

PN should be used as second line treatment in patients who cannot be fed adequately by oral and/or EN
Grade of Recommendation GPP – Consensus (90% agreement)

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 documented above (Recommendation 8 and comments) 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 [180].

4.5. In ALF patients on EN, what is the evidence to use specialized formula compared to standard formula to achieve a. better survival, b. less complications, c. improve metabolism?

Recommendation 14

Standard enteral formulas can be given, as there are no data regarding the value of a disease specific composition.
Grade of Recommendation GPP – Strong consensus (100% agreement)

Commentary

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 [176,180].

5. Alcoholic steatohepatitis

5.1. In patients with severe ASH, when is nutrition therapy indicated in order to a. reduce the risk for comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 15

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. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

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 [110,111,142,181]. Presence of malnutrition is an independent predictor of mortality and adversely affects response to corticosteroids and oxandrolone only in moderate but not severe ASH [110,182,183]. 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 HE and improvement in liver function. Overall survival advantage of nutritional supplementation has been reported in some studies, but systematic reviews/meta-analyses have not shown a survival benefit. In the most recent multicenter study, irrespective of treatment, lower calorie intake (21.5 kcal $\times$ kg^{-1} $\times$ d^{-1}) was associated with worse clinical outcomes [113,184]. Calorie intake is significantly reduced even in the abstinent ASH patients, and increased caloric intake improves outcomes [110,185], 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. Whether the reduced caloric intake results in or contributes to the higher mortality in those patients achieving only a lower caloric intake or whether the reduction in spontaneous intake is an outcome of underlying necroinflammatory responses that contribute to higher mortality is not known and should be part of future evaluations.

5.2. In patients with severe ASH, can nutrition therapy by means of ONS with/without nutrition counselling when compared to spontaneous ad lib eating a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 16

ONS should be used when patients with severe ASH cannot meet their caloric requirements through normal food in order to improve survival (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

In patients with severe alcoholic hepatitis, oral intake is consistently reduced [110,111,142,181]. 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 [186–188]. Enteral or supplemental feeding has been evaluated in severe alcoholic hepatitis, but no mortality benefit has been consistently reported. In the VA studies, a survival advantage to supplemental nutrition was reported in patients with malnutrition. In a meta-analysis of 13 randomized controlled trials, that included both ASH and patients with jaundiced alcoholic cirrhosis who may have had ASH, random effects analysis showed a reduction in mortality with supplemental nutrition. However, whether specifically, oral nutritional support will provide such a benefit cannot be stated with certainty. It must also be noted that in the same meta-analysis, a sequential analysis of the same data did not validate the improvement in mortality. A Cochrane review that included alcoholic and non-alcoholic liver disease concluded that any supplemental nutritional intervention did not influence mortality. Interestingly, there did not seem to be a benefit in alcoholic

liver disease compared to other forms of liver disease. The confounding effects of including non-alcoholic patients and those with cirrhosis on the interpretation need to be taken into consideration. Finally, another meta-analysis of hospitalized patients with alcoholic liver disease, the majority of whom had ASH, showed no mortality benefit on pooled analysis. 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 [113], 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 [188].

Recommendation 17

Patients should be fed orally as long as cough and swallow reflexes are intact, and energy and protein goal intakes can be achieved.

Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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 [110,111,142,181]. 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 [189]. 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.

5.3. In patients with severe ASH, can nutrition therapy by means of EN when compared to spontaneous ad lib eating a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 18

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. (BM)

Grade of recommendation B – Strong consensus (100% agreement)

Commentary

When caloric intake is reduced, mortality is higher in severe ASH [113]. Supplementing extra calories does not improve survival in most randomized studies but in patients with malnutrition, a survival advantage was reported in the VA studies. Similarly, in one meta-analysis, random effects analysis showed a survival advantage and lower infection rates [188]. 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 [110]. 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. Progression to cirrhosis has not been evaluated but a histological study on nutritional supplementation showed that abstinence was the major factor that resulted in histological improvement in ASH.

5.4. In patients with severe ASH, can nutrition therapy by means of PN when compared to spontaneous ad lib eating a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 19

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.

Grade of recommendation GPP - Strong consensus (100% agreement)

Commentary

Malnourished patients with severe ASH have worse clinical outcomes in terms of one- and six-month survival, infection rates, HE and laboratory parameters [110,142,181]. Lower calorie intake is associated with increased rates of liver related complications including infection, ascites, HE and jaundice. A number of publications including randomized controlled trials show that nutritional supplementation with amino acid mixtures or calories lowers infection rates and resolution of HE but the beneficial effects on survival was only reported in patients with moderate ASH but not in severe ASH [182,183,185,187,188,190]. In severe ASH, malnutrition, specifically measures of muscle loss, are associated with increased mortality, infection and HE [186–188].

PN can include amino acids and/or glucose infusion, peripheral or central PN to support dietary intakes in patients whose oral intake is insufficient. Eight studies have evaluated different parenteral supplements, mostly amino acid or glucose infusion, seven of which were randomized in ASH [182,183,185,191–196]. One study showed a survival advantage of intravenous amino acids but this has never been reproduced in any other study [185]. 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 [187] or of Mallory hyaline [195]. 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 HE [187,188]. Spontaneous ad lib eating was associated with reduced intake in both the US VA studies and non-VA studies [110,111,142,181,184,193]. As discussed earlier and based on published literature, poor oral intake is associated with adverse outcomes. Additionally, patients with moderate and severe ASH are hyper-metabolic when REE is corrected for urinary creatinine as a measure of lean body mass [69]. To overcome the hyper-metabolic state, if patients do not achieve an adequate caloric and protein intake orally, PN needs to be started as soon as possible. A previous

report has also shown better survival with supplemental EN, but such stratified results have not been reported with PN [110]. Hence, there is sufficient rationale to start PN in patients with severe ASH who do not have adequate intake orally.

Recommendation 20

PN should be considered in patients with unprotected airways and HE when cough and swallow reflexes are compromised or EN is contraindicated or impracticable.
Grade of recommendation GPP – Majority agreement (72% agreement)

Commentary

There is no direct evidence evaluating the role of PN in the subgroup of patients with HE and/or unprotected airways with impaired protective reflexes [4,5,186–189,197]. Even though the use of PN in encephalopathic or critically ill patients with impaired cough or gag reflex is recommended by some [4], there are others who do not believe in the use of PN for ASH [197].

5.5. In patients with severe ASH, can disease specific nutrition protocols regarding quantity and/or composition of protein/amino acids when compared to no such protocols a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 21

For ONS or EN in patients with severe ASH standard formulas should be used, preferably formulas with high energy density ($\geq$1.5 kcal $\times$ ml^{-1}).
Grade of recommendation GPP – Strong consensus (92% agreement)

Commentary

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 [198]. Immunonutrition was reported to provide no specific therapeutic advantage in a randomized controlled trial in patients undergoing LT [199]. In severe ASH, there are no controlled trials showing a benefit of specially composed formula over a standard formula [194,200,201]. 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.

5.6. In patients with severe ASH, can disease specific nutrition protocols regarding quantity and/or composition of micronutrients when compared to no such protocols a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Statement 12

In patients with severe ASH trace element and vitamin deficiency should be anticipated.
Strong consensus (100% agreement)

Commentary

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 [134,182,183,198,202–207]. 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. It is not known if correcting deficiency can prevent infection or mortality but given the strong evidence for adverse consequences of micronutrient deficiency, one should consider replacement if deficiency is known or determined. However, micronutrient deficiencies are frequent in patients with alcohol use disorders and thiamine supplementation is used routinely in clinical practice to prevent Wernicke's encephalopathy and Korsakoff psychosis. There are very limited randomized trials in patients with alcoholic liver disease but none in severe ASH. Since patients with severe ASH have poor dietary intake and micronutrient deficiency can affect immune and gut mucosal function, it is reasonable to replace micronutrients. 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. A recent study suggested that in patients at risk for Wernicke's encephalopathy, thiamin rather than a mixed formulary of micronutrients be administered [205]. Similar data do not exist for other vitamin or zinc deficiencies in human ASH. The cost of measuring micronutrient deficiencies vs. that of the replacement should be considered in making this decision. Some micronutrient and vitamin excesses may be injurious when administered in the long-term. If long-term supplementation is planned, then consideration for measuring serum concentrations may be of value.

Recommendation 22

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.
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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 [208–210]. Specific vitamins, including vitamin A, D and K should be administered along with thiamine, folate and pyridoxine to correct deficiency.

5.7. In patients with severe ASH, how should nutrition therapy by means of ONS with/without nutritional counselling be delivered in order to a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 23

Individualized nutrition counselling should be used in order to improve food intake.
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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

Recommendation 24

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.
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

Reduced oral intake is associated with higher mortality and nutritional supplementation is likely to result in more rapid resolution of HE 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. Whether alcoholic hepatitis is a state of accelerated starvation akin to cirrhosis has not been directly reported, metabolomic studies and metabolic cart studies suggest hyper-metabolism, accelerated lipolysis and accelerated starvation physiology in ASH [69,72,211]. Since compelling data for a late evening snack have been reported in LC including alcoholic cirrhosis [212], it is reasonable to extend these data to support the use of a late evening or nocturnal supplements to reduce the duration of starvation.

5.8. In patients with severe ASH, how should nutrition therapy by means of EN be delivered in order to a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 25

EN can be used in severe ASH to ensure adequate energy and protein intake without increasing the risk of HE. (BM)
Grade of recommendation 0 – Strong consensus (92% agreement)

Commentary

EN has proved successful in providing patients with alcoholic cirrhosis [190] or cirrhosis with HE grade I-III [213] 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 [213]. In another study 16 patients were given 1.5 g kg^{-1} d^{-1} protein using a casein based enteral formula [190]. Likewise, in 136 patients of the VA trials low protein intake was associated with worsening HE while patients with a higher protein intake showed improved mental state [214].

Recommendation 26

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 (BM).
Grade of recommendation B – Consensus (85% agreement)

Commentary

An initial randomized study comparing steroids alone with total EN showed no difference in mortality on an intention to treat analysis but earlier mortality in steroid treated subjects [184]. Even though mortality in the patients with HE was similar in the EN and steroid treated arms, whether the resolution of HE was different was not reported [184]. Other studies on EN also reported no survival benefit but EN resulted in greater improvement in HE and reduction in bilirubin [190]. A more recent study compared EN or conventional nutrition in patients with severe ASH all of whom received steroids. No difference in mortality was observed at six months. Daily caloric intake of <21.5 kcal kg^{-1} d^{-1} was associated with higher mortality at one and six months and higher risk of infection and a trend towards higher risk of hepatorenal syndrome without a significant impact on HE [113].

Even though the benefit of steroids in severe ASH has been questioned [215], 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 [184]. The authors concluded that a synergistic effect of steroids and EN in severe ASH needed 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 [113]. However, lower caloric intake did increase mortality in both groups suggesting that EN may provide a survival advantage early in ASH [113,184].

5.9. In patients with severe ASH, how should nutrition therapy by means of PN be delivered in order to a. reduce the risk of comorbidity (e.g. infection, HE, multi-organ failure), b. improve liver function, c. improve ASH histology, d. slow progression to cirrhosis, e. reduce mortality?

Recommendation 27

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 twelve hours, should be given i. v. glucose at 2–3 g $\times$ kg^{-1} $\times$ d^{-1}. When this fasting period lasts longer than 72 h total PN is required.
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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 [216–219]. 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 twelve hours and timely institute the infusion of glucose or peripheral hypocaloric PN.

There is no data to determine the type or rate of administration of PN in patients with severe ASH. Parenteral amino acids have been shown to result in more rapid resolution of fatty infiltration [193] and alcoholic hyaline [195]. 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.

Recommendation 28

In patients with severe ASH, PN should be delivered like in other critically ill patients.
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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.

6. Non-alcoholic fatty liver disease

6.1. In overweight/obese patients with NAFL/NASH, what are the aims of nutritional therapy?

Recommendation 29

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. (BM)
Grade of recommendation A – Strong consensus (96% agreement)

Commentary

Weight loss generally reduces hepatic steatosis, irrespective of how it is achieved [119,120,220]. However, longitudinal studies of patients with NAFLD clearly show that fibrosis stage, but no other histologic features of steatohepatitis, is associated independently with long-term overall mortality, liver transplantation, and liver-related events [221]. 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 [222–230]. A less pronounced weight loss is associated with improvement in steatosis, inflammation and liver enzymes, but not in fibrosis [230–234].

A meta-analysis of 15 studies reporting findings from 766 paired liver biopsies of patients losing weight after bariatric surgery shows improvement or resolution in steatosis in 91.6% (95% CI, 82.4–97.6%), in steatohepatitis in 81.3% (95% CI, 61.9–94.9%), in fibrosis in 65.5% (95% CI, 38.2–88.1%) [235]. NASH resolved completely in 69.5% (95% CI, 42.4–90.8%). In this pooled sample mean BMI reduction ranged from 19.1 to 41.7%. The potential of bariatric surgery to improve fibrosis of NASH is underscored by another meta-analysis [236]. A less invasive procedure, endoscopic placement of a duodeno-jejunal bypass liner for six months, resulted in 10.9% weight loss accompanied by a decrease in liver enzymes [237].

Recommendation 30

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. (BM)
Grade of recommendation A – Strong consensus (100% agreement)

Commentary

Life style change resulting in moderate weight loss (< 5 %) was shown to improve hepatic fat accumulation as detected by ^{1}H-MRS only when hypocaloric diet and exercise but not when hypocaloric diet alone were implemented [238,239]. Life style change resulting in weight loss of 5–10 % was shown to improve histology when hypocaloric diet and exercise were implemented [225,230,233,240,241]. 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 > 7–9 % was achieved [225,233,241] while only a weight loss > 10 % was associated with improvement in fibrosis [230]. 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 [242].

Available data indicate also, that each of the two interventions alone is effective when the other variable - either weight or daily physical activity - is kept constant. Non-invasive measurements using ^{1}H-MR-spectroscopy convincingly demonstrate a reduction of intrahepatic and visceral triglycerides in subjects just exercising without losing weight [243–245] or following intensive lifestyle intervention by moderate caloric restriction and exercise [246]. Conversely, weight loss by either a low carb or a low-fat diet in subjects maintaining their sedentary lifestyle was associated with a substantial loss of intrahepatic lipid [231].

NAFLD patients have a low level of physical activity and, when they have diabetes mellitus, they perform at the lowest quartile of physical activity [247]. Readiness for behavior changes, however, is low in overweight/obese patients with NAFLD with only 10 % actively working on or preparing to change [248].

6.2. In normal weight patients with NAFL/NASH, what are the aims of nutritional therapy?

Recommendation 31

In normal weight NAFL/NASH patients, increased physical activity to improve insulin resistance and steatosis can be recommended. (BM)
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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 [243–245,249] 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.

6.3. For overweight/obese patients with NAFL/NASH, which oral diet (low energy, low carb, low fat) when compared to a normal oral diet can be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 32

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). (BM)
Grade of recommendation A – Strong consensus (100% agreement)

Recommendation 33

In order to achieve weight loss, a hypocaloric diet shall be followed according to current obesity guidelines irrespective of the macronutrient composition. (BM)
Grade of recommendation A – Strong consensus (93% agreement)

Commentary to recommendations 32 and 33

In general, nutrition counseling of overweight and obese NAFLD patients should be done in accordance with current guidelines for the dietary management of obesity [250–252]. As outlined above, weight reduction and lifestyle interventions reduce hepatic steatosis and liver injury. As yet, 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 [253]. The authors of this umbrella review of meta-analyses correctly point out that robust randomized controlled trials are needed to understand whether the observed associations are causal [253].

In a multi-center randomized study, very-low-calorie diets were effective and safe in reducing body weight and improving NAFLD within twelve weeks [254]. Likewise, a low-calorie diet was effective in achieving weight loss of at least 5 % and improvement of NAFLD [242,246,255]. 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 [256,257] while Kirk et al. reported the same decrease in intrahepatic lipid after 11 weeks on either a low or a high carbohydrate diet [258]. Moreover, another trial showed the same beneficial effects regardless of whether the diet was low fat or a low carb [231]. Two trials report beneficial effects of a diet low in saturated fat [259,260]. In a prospective study in obese diabetics comparing isocaloric diets high in animal or plant protein a decrease in intrahepatic fat (by MR spectroscopy) and insulin resistance (by hyper-insulinemic euglycemic clamp) was observed after 6 weeks [261]; in the study period BMI decreased significantly, too.

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 [262,263]. Increased fructose consumption as well as hepatic fructokinase and fatty acid synthase mRNA have been observed in NAFLD patients when compared to controls [264]. 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 [119,265]. The authors of recent meta-analyses summarize, however, that the available evidence was not sufficiently robust to draw conclusions regarding NAFLD promoting effects specific to fructose when consumed as ingredient of a normocaloric diet [266,267]. Likewise, in a double-blind trial, a hyper-caloric diet but not fructose when compared to isocaloric glucose was associated with an increase in hepatic lipid and ALT levels in overweight men [268].

6.4. For patients with NAFL/NASH, can a Mediterranean diet when compared to a western type diet be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 34

A Mediterranean diet should be advised to improve steatosis and insulin sensitivity. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

Seven interventional [269–275] and five observational [276–280] studies are available suggesting that a Mediterranean diet (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 [119,281,282]. 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 [283]. Higher adherence to the MEDD is not associated with a lower likelihood of having NAFLD, but it is associated with a lower degree of insulin resistance and less severe liver disease among patients with NAFLD [278].

Even without weight loss, MEDD reduces liver steatosis and improves insulin sensitivity in an insulin-resistant population with NAFLD, compared to current dietary advice [273]. Using whole-body MRI, the investigators of the CENTRAL trial [284] found that the MEDD, rich in unsaturated fats and low in carbohydrates, is superior to the low-fat diet in mobilizing specific ectopic fat depots as hepatic, cardiac, and pancreatic fats. In an analysis of participants in the Framingham Heart Study, increasing diet quality as assessed by Mediterranean Diet Score is associated with less liver fat accumulation and reduced risk for new-onset NAFLD [285]. In addition, the authors found that an improved diet is particularly important for individuals with a high genetic risk for NAFLD. The investigators of the MEDINA trial demonstrated in a cohort of patients with NALFD

that MEDD independent of weight loss can result in significant benefits in liver fat and insulin sensitivity and that these changes are sustained at twelve months [286].

6.5. For patients with NAFL/NASH, can life style intervention by physical exercise and/or reduced/cut alcohol consumption when compared to no life style intervention be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 35

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. (BM)
Grade of recommendation A – Strong consensus (100% agreement)

Commentary

Non-invasive measurements using ^{1}H-MR-spectroscopy convincingly demonstrate a reduction of intrahepatic and visceral triglycerides in subjects just exercising without losing weight [243–245]. Three months of resistance training improved the hepatorenal-ultrasound index (HRI) as a readout of hepatic steatosis but did not affect liver enzymes, serum triglycerides or HOMA-IR [249]. 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.

Recommendation 36

NAFL/NASH patients shall be encouraged to abstain from alcohol in order reduce risk for comorbidity and to improve liver biochemistry and histology. (BM).
Grade of recommendation A – Strong consensus (100% agreement)

Commentary

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 [287]. From their findings 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 [287]. 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 [288]. These findings were not included in the AASLD/AG [120] and EASL/EASD/EASO [119] guidelines recommending only to abstain from heavy amounts of alcohol. Until evidence from intervention studies is available it seems unjustified to suggest a potential health benefit from moderate alcohol consumption on NAFL/NASH [119,120].

6.6. For celiac disease patients with NAFL/NASH, can a gluten free diet when compared to a normal diet be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 37

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. (BM)
Grade of recommendation B – Strong consensus (96% agreement)

Commentary

Celiac disease is a model condition for studying the close interaction between gut and liver [289]. Liver injury in celiac disease ranges from mildly elevated transaminases to NAFLD and (rarely) cirrhosis [290–294]. Elevation of transaminases has been reported in 40% of adults and in 54% of children at the time of diagnosis of celiac disease and, conversely, celiac disease is present in about 9% of patients with chronic unexplained elevation of transaminases [291,295,296]. Celiac disease is twice as common in patients with cirrhosis than in the general population [297]. Celiac disease patients are at increased risk of liver disease prior to or subsequent to the diagnosis of celiac disease [290]. According to a systematic analysis [298] 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 % [299] upon institution of a gluten free diet [300–306]. 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 [307]. Of five US patients with LC 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 [297]. 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 [291,299].

6.7. For patients with NAFL/NASH, can vitamin E supplementation when compared to no such supplementation be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 38

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. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

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 [241,308–317]. 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 [119,120]: 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 d^{-1} for two years) compared to placebo (42% vs. 19%, $p < 0.001$, number needed to treat = 4.4) [315]. 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 [318]. Interestingly, vitamin E had an added effect on the improvement of ALT, NAS, and fibrosis scores obtained by weight loss ≥2.0 kg [318].

The authors of a meta-analysis of 19 trials (135 967 participants) studying a variety of populations in whom the presence or absence of NASH was not specifically addressed came to the conclusion that vitamin E dosage ≥ 400 IU d^{-1} was associated with an increased risk for all-cause mortality and should be avoided [319]. This issue is also discussed in the in the light of more recent findings [120].The Cochrane Hepato-Biliary Group's meta-analysis of 20 randomized trials (1225 participants) studying the effect of anti-oxidant supplements in patients with liver disease of various etiology included 15 trials supplementing vitamin E [320]. The authors found no significant treatment effect of antioxidants on all-cause mortality or liver-related mortality. In another meta-analysis no beneficial effect of anti-oxidant treatment on liver biochemistry and histology was reported [321]. In their meta-analysis Ji et al. report an effect of vitamin E on ALT and AST in NASH but not in NAFLD [322]. Of the two large and well controlled trials in NASH patients with neither diabetes nor cirrhosis the abstract of the PIVENS trial was included in one meta-analysis only [321] and the TONIC trial [313] in none.

6.8. For patients with NAFL/NASH, can supplementation with anti-oxidants when compared to no such supplementation be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 39

Until further data regarding their efficacy are available, antioxidants (e.g. vitamin C, resveratrol, anthocyanin, bayberries) cannot be recommended to treat NAFL/NASH. (BM)

Grade of recommendation 0 – Strong consensus (100% agreement)

Commentary

In twelve overweight/obese men with NAFLD, 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 [323]. In a randomized controlled 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 in 30 normal weight men with NAFLD on ultrasound [324]. 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; this randomized controlled trial obviously was published in duplicate [325,326].

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 [327].

In a randomized controlled pilot trial, the flavonoid anthocyanin (320 mg p. o. for twelve weeks) decreased ALT and the 2-hour loading glucose level [328].

Oral coenzyme Q10 supplementation was reported to reduce waist circumference, serum AST levels and blood total anti-oxidant capacity [329].

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 [330].

Abnormally low choline levels have been implicated in the pathogenesis of PN associated liver disease of which some morphological features resemble NAFLD/NASH [331]. 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 [332]. Along this line, data from the Shanghai Women's and Men's Health Study suggest that higher dietary choline intake may be associated with a lower risk of NAFLD [333]. 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 [334]. 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 [335]. 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 [336]. These are preliminary results and, therefore L-carnitine cannot be recommended yet.

6.9. For patients with NAFL/NASH, can supplementation with omega-3 fatty acids when compared to no such supplementation be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 40

Until further data regarding their efficacy are available, omega-3-fatty acids cannot be recommended to treat NAFL/NASH. (BM)

Grade of recommendation 0 – Strong consensus (100% agreement)

Commentary

Fish oil has the potential to maintain proper insulin signaling in the brain, ameliorate NAFLD and decrease the risk to metabolic syndrome suggesting that adequate levels of omega-3 fatty acids in the diet can attenuate or neutralize the metabolic challenges imposed by Western lifestyle [337]. 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 [338]. 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 [339]. In a smaller controlled trial, 3 g of omega-3 fatty acids improved hepatic fat content but failed to improve NAS by 2 points [340]. 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 [341]. In 20 children paired biopsies showed improved histological NAFLD score after 18 months on docosahexaenoic acid [342].

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 [343]. 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 [344]. In twelve of the seventeen published human studies the supplementation with n-3 PUFAs was accompanied by a decrease in liver fat and/or other markers of NAFLD. Five studies, including the largest study [339] were negative. 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 [345].

6.10. For patients with NAFL/NASH, are there other nutrition supplements which can be recommended to a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce incidence of HCC, f. reduce mortality?

Recommendation 41

Nutritional supplements containing selected probiotics or synbiotics can be used to improve liver enzymes in NAFL/NASH patients. (BM)
Grade of recommendation 0 − Consensus (89% agreement)

Commentary

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 [346]. 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 [347]. 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 [348].

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 [349]. In a randomized, double-blind, placebo-controlled clinical trial, 52 patients with NAFLD (by ultrasound) 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 [350]. 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 [351].

6.11. In patients with NAFL/NASH, when is nutritional therapy using EN and/or PN indicated to prevent/reduce mortality and morbidity due to malnutrition (e.g. sarcopenic obesity)?

Recommendation 42

EN or PN shall be administered in NAFL/NASH patients during severe intercurrent illness, when oral nutrition alone is inadequate or impossible or contraindicated.
Grade of recommendation GPP- Strong consensus (96% agreement)

6.12. In normal weight/overweight patients with NAFL/NASH, in which dosage should energy/protein/nutrition supplements by EN and/or PN be given to a. preserve lean body mass, b. protect from or improve sarcopenia, c. reduce inflammation, d. improve morbidity, e. improve mortality?

Recommendation 43

In NAFL/NASH patients with a BMI < 30 kg/m^2 EN and/or PN should be done as recommended for ASH patients (see recommendations 18, 19, 20, 25, 27, 28).
Grade of recommendation GPP − Strong consensus (100% agreement)

Commentary to recommendations 42 and 43

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 [352]. 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 LC 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.

6.13. In obese patients with NAFL/NASH, in which dosage should energy/protein/nutrition supplements by EN and/or PN be given to a. preserve lean body mass, b. protect from or improve sarcopenia, c. reduce inflammation, d. improve morbidity, e. improve mortality?

Recommendation 44

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}.

Grade of recommendation GPP – Majority agreement (71% agreement)

Commentary

An increasing number (30–35 %) of adult ICU patients are obese and at least 5 % are morbidly obese [353]. 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 $g \cdot kg^{-1}$ $IBW \cdot d^{-1}$) for the preservation of lean body mass but a hypocaloric regimen (25 $kcal \cdot kg^{-1}$ $IBW \cdot d^{-1}$) aiming for the reduction of fat mass and insulin resistance [354]. A recent NutritionDay analysis reveals that current practice of nutrition in participating ICUs by far fails to achieve the ASPEN targets [355]. No recommendation specific for nutrition support of obese ICU patients is made in the current ESICM guidelines on early EN [179]. 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.

6.14. In overweight/obese patients with NAFL/NASH, under which conditions is bariatric surgery indicated/contraindicated to achieve weight reduction?

Recommendation 45

In otherwise eligible obese NAFL/NASH patients without cirrhosis, after weight reduction diets and intensive lifestyle interventions have failed, bariatric surgery should be proposed. (BM)

Grade of recommendation B – Strong consensus (100% agreement)

Commentary

Lifestyle intervention, although effective in some patients, is not sufficient to achieve long-term weight loss and resolution of NASH. It is estimated that only 10 % of patients who commit to a lifestyle intervention lose more than 10% of their weight, even when the intervention involves a multidisciplinary approach [356]. 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. Indeed, the majority of obese patients undergoing bariatric surgery are obese and have associated NAFLD [120]. 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% [235]. These findings are corroborated by the Lille data from France [227]. Using a state-transition model, Klebanoff et al. [357] aimed to assess the effectiveness and cost-effectiveness of surgery or intensive lifestyle intervention to manage NASH. Both interventions increased QALYs compared to no intervention. Surgery was both effective and cost-effective for obese patients with NASH, regardless of fibrosis stage F0-F3. In overweight patients, surgery increased QALYs for all patients regardless of fibrosis stage, but it was cost-effective only for patients with F3 fibrosis.

In one series, cirrhosis was diagnosed intraoperatively in 4 % and fibrosis in 37 % of patients undergoing bariatric surgery [358]. 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 %) [359].

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 [119].

6.15. In obese patients with NAFL/NASH, can bariatric surgery when compared to weight losing diet with/without counselling a. reduce the risk for comorbidity (e.g. cardiovascular, diabetes), b. improve liver enzymes, c. improve NASH histology, d. slow progression to cirrhosis, e. reduce the incidence of HCC, f. reduce mortality?

Statement 13

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. (BM)

Strong consensus (100% agreement)

Commentary

The effect of bariatric surgery on liver histology in paired biopsies has been reported in 16 studies [222–224,227,228,360–370]. 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 [221]. Also, insulin sensitivity is improved, and a considerable proportion of diabetic patients needs no more antidiabetic treatment. As to the type of bariatric surgery, a greater efficacy of gastric bypass when compared to gastric banding should be considered regarding the improvement in liver pathology as well as insulin resistance [223].

7. Cirrhosis

7.1. In cirrhotic patients, should specific nutritional counselling when compared to no nutritional counseling be used to improve patients' outcome and/or survival?

Recommendation 46

Specific nutritional counselling should be implemented in cirrhotic patients using a multidisciplinary team to improve patients' long-term outcome/survival. (BM)

Grade of recommendation GPP – Strong consensus (100% agreement)

Recommendation 47

Multidisciplinary nutrition care should include monitoring of nutritional status and provide guidance for achieving nutritional goals. (BM)

Grade of recommendation GPP – Strong consensus (95% agreement)

Commentary to recommendations 46 and 47

Nutrition therapy should be included in the management of LC 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 LC patients received specialized nutrition counseling as compared to no counseling [371]. 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 [371].

7.2. In cirrhotic patients, can nutritional intervention (either oral, EN or PN) when compared to no such intervention ameliorate outcome and survival?

Recommendation 48

In cirrhotic patients, nutritional intervention (either oral, EN or PN) shall be implemented according to current guidelines for non-cirrhotic patients. (BM)
Grade of recommendation A – Consensus (89% agreement)

Recommendation 49

In cirrhotic patients, nutritional intervention (either oral or EN or PN) should be recommended for potential clinical benefit without an increase in adverse events.
Grade of recommendation GPP– Strong consensus (100% agreement)

Commentary to recommendations 48 and 49

In principle, the differential indications for oral nutrition, EN or PN in LC patients are not different from those covered in guidelines for non-cirrhotic patients. It should be noted, however, that LC 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 general). Therefore, the timely institution of nutrition is of prime importance to provide metabolic fuel and substrate for protein anabolism.

As commented in detail regarding recommendations 58–64 a number of studies on nutrition therapy in LC patients showed improved clinical outcome including survival. Recent meta-analyses, however, fail to confirm a survival benefit [186–188,372]. Methodologically, these meta-analyses suffer from various flaws like mixing LC and ASH or including trials with just three days of nutrition or excluding pertinent trials for no obvious reason.

7.3. In cirrhotic patients, is an increased energy regimen always indicated vs a normal energy regimen to meet energy need?

Recommendation 50

Cirrhotic patients in conditions of increased energy expenditure (i. e. acute complications, refractory ascites) or malnutrition, should ingest an increased amount of energy. (BM)
Grade of recommendation GPP– Strong consensus (100% agreement)

Recommendation 51

In cirrhotic patients, an increased energy intake is not recommended in overweight or obese patients. (BM)
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary to recommendations 50 and 51

In general, energy requirements in compensated LC patients are not higher than in healthy individuals (see statement 4 and recommendation 2). Moreover, LC patients have a decreased physical activity level [82,96] 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 [88,190]. This is of special relevance in the subgroup (up to 35% of LC patients) of hyper-metabolic LC patients [33,79,80] 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, enteral or parenteral nutrition 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 [190].

The proportion of overweight or obese LC patients has increased even in cohorts on the wait list for transplantation [101,169,373]. In chronic liver disease, obesity has been identified as an independent risk factor for a worse clinical outcome [374,375]. 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 LC patients [376]. Therefore, an increased energy intake is not recommended in obese cirrhotic patients.

7.4. In all cirrhotic patients, is increased as compared to normal protein assumption/intake always needed to face increased protein turnover and catabolism?

Recommendation 52

Non-malnourished patients with compensated cirrhosis should ingest 1.2 $g \cdot kg^{-1} \cdot d^{-1}$ protein. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 53

To replenish malnourished and/or sarcopenic cirrhotic patients the amount of 1.5 $g \cdot kg^{-1} \cdot d^{-1}$ protein should be ingested. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary to recommendations 52 and 53

LC patients can effectively accrete protein but require an increased amount of protein to achieve nitrogen balance [64]. In a small study protein requirements were found to be elevated in eight cirrhotic patients and the authors recommend to always supply 60 g of protein per day in these patients [218]. No trials or intervention studies are available for well-nourished compensated cirrhotic patients.

Malnourished and sarcopenic cirrhotic patients experience protein depletion both due to elevated total body protein breakdown and decreased protein synthesis in muscle [14,377–380]. Increased protein intake is generally well tolerated and safe in cirrhotic patients and ameliorates protein anabolism as shown in previous studies [64,218]. Adequate refeeding was able to induce a significant increase of protein synthesis in a small group of carefully

followed malnourished cirrhotic patients [381]. 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 [150,382–385]. An improvement in total body protein status was observed, when ONS were consumed nocturnally [219] extending previous observations of a beneficial effect of a late evening carbohydrate or protein snack in LC patients [216–218].

7.5. In cirrhotic patients with HE, is protein restriction indicated to ameliorate HE?

Recommendation 54

Protein intake should not be restricted in cirrhotic patients with HE as it increases protein catabolism. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

A very select subgroup of LC patients, termed protein intolerant, develop encephalopathy on a normal protein intake [386,387] 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 HE [190,214,381,388]. As shown in a RCT by Cordoba et al. [389] protein restriction has no advantage on the clinical course of acute HE and may increase protein catabolism. After this study the dogma of prescribing protein restriction for LC patients with HE was definitively abandoned, and all efforts were focused on achieving an adequate protein intake in these patients.

7.6. In cirrhotic patients, is micronutrient supplementation always needed to correct alterations?

Recommendation 55

In cirrhotic patients, micronutrients should be administered to treat confirmed or clinically suspected deficiency. (BM)
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

Patients with cirrhosis may present deficiencies in water-soluble vitamins, particularly thiamine, and lipid soluble vitamins such as vitamin D [390,391]. There are no reports which systematically evaluate the requirement of micronutrients in LC. 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 [392,393]. Zinc and selenium deficiency have been observed in patients with alcoholic as well as non-alcoholic liver disease [394–396]. An impressive association between HE and zinc deficiency has been described in case reports [397,398]. Randomized controlled trials, however, showed no therapeutic effect of oral zinc supplementation on HE [399–401]. Oral zinc supplementation can increase urea production capacity when previously subnormal plasma levels are normalized [402].

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 LC patients are at risk for developing refeeding syndrome and thiamine deficiency.

7.7. In obese patients with cirrhosis, can a program of weight reduction ameliorate outcome and survival?

Recommendation 56

In obese patients with cirrhosis lifestyle intervention aiming for beneficial effects of weight reduction, which include reduced portal hypertension, should be implemented. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

In a recent multicenter uncontrolled study [376], the response to hypocaloric normonitrogenous diet and 60 min/wk. of supervised physical activity for 16 weeks was evaluated in 50 overweight/obese (BMI $\geq$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.

7.8. In cirrhotic patients with malnutrition and/or sarcopenia, can quantitative and qualitative modification of the oral diet and pattern of food intake ameliorate nutritional status, muscle mass, outcome, survival?

Recommendation 57

Oral diet of cirrhotic patients with malnutrition and muscle depletion should provide 30–35 kcal $\times$ kg^{-1} $\times$ d^{-1} and 1.5 g protein $\times$ kg^{-1} $\times$ d^{-1}. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 58

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. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 59

In cirrhotic patients who are protein "intolerant", vegetable proteins or BCAA (0.25 g $\times$ kg^{-1} $\times$ d^{-1}) should be used by oral route to facilitate adequate protein intake. (BM).
Grade of recommendation B – Consensus (89% agreement)

Recommendation 60

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 (BM)

Grade of recommendation B – Consensus (89% agreement)

Recommendation 61

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. (BM). Care should be taken to avoid compromising the palatability of the diet after sodium reduction.

Grade of recommendation GPP – Consensus (78% agreement)

Commentary to recommendations 57–61

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}. Excluding trials using BCAA-enriched ONS a meta-analysis found a reduced mortality in a subgroup analysis [372]. After successful treatment of portal hypertension by transjugular intrahepatic stent-shunt (TIPS), LC patients on normal food (according to ESPEN recommendations) were able to improve their body composition [81,403].

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 [219]. Previously, a late evening carbohydrate snack has been shown to improve protein metabolism in LC [216,217,404]. In their systematic review Tsien and coworkers [212] 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.

In the very rare case of a "protein intolerant" LC patient developing encephalopathy when ingesting normal amounts of mixed protein, a vegetable protein diet may be beneficial. A number of reviews have addressed this issue [405–407] but there is no data from randomized controlled trials comparing isocaloric and isonitrogenous regimens. One study [408] was uncontrolled and in a more recent study nutritional therapy using a vegetable protein diet was compared to no therapy [409].

There are no data available from trials comparing a standard enteral formula and an enteral formula enriched in BCAA in LC patients. BCAA-enriched formulas, however, have been used in trials demonstrating improved survival in severely malnourished ASH and LC patients [110,111,388,410] or mental state in a highly selected group of protein intolerant LC patients with encephalopathy [386]. 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 [411,412]. In LC patients after an episode of HE, BCAA supplementation for twelve months improved minimal HE and muscle mass but the recurrence of overt HE was not decreased vs the control group [413]. In a retrospective analysis, BCAA supplementation was associated with better survival in sarcopenic but not in non-sarcopenic LC patients [410]. In trials reporting beneficial effects on mental state and/or protein metabolism BCAA were given at doses of 0.20–0.25 g·kgBW^{-1}·d^{-1} [411,412,414,415] or 30 g·d^{-1} [386,413]. In a Cochrane meta-analysis, overall a beneficial effect of BCAA on mental state was found [416] but there are unresolved issues regarding trial methodology [417,418]. In most countries, however, oral BCAA supplements are not reimbursed and the combination of cost and palatability may affect compliance.

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 [419,420]. Therefore, great care should be taken to ensure adequate nutrition when prescribing a sodium restricted diet. In ascitic LC 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 [421].

7.9. In cirrhotic patients, can EN ameliorate nutritional status, muscle mass, outcome, survival?

Recommendation 62

In cirrhotic patients, who cannot be fed orally or who do not reach the nutritional target through the oral diet, EN should be performed. (BM)

Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 63

Esophageal varices are no absolute contraindication for positioning a nasogastric tube (BM)

Grade of recommendation 0 – Strong consensus (100% agreement)

Recommendation 64

PEG placement is associated with a higher risk of complications, due to ascites or varices, and thus, can only be used in exceptional cases. (BM)

Grade of recommendation 0 – Strong consensus (100% agreement)

Commentary to recommendations 62–64

There is ample evidence indicating that ensuring a quantitatively adequate nutrient intake should be the primary goal [61,145,190,201,382,384,385,388,422]. If nutritional requirements cannot be met by oral nutrition alone or in combination with ONS then EN is required. EN and has been shown to improve survival and liver function [190,201,388]. 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 [423]. 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 [372] find 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 [424] and for the exclusion of two relevant controlled trials [190,388] for no good reasons.

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In ten patients with acute HE I-II nasogastric tube feeding using a BCAA-enriched enteral formula was successful with regard to recovery from HE without any complication due to variceal bleeding [213]. There is no evidence in the current literature [184,190,388,424–426] that esophageal varices pose an unacceptable risk to the use of fine bore nasogastric tubes for EN.

Regarding the placement of a percutaneous endoscopic gastrostomy (PEG) feeding tube the current European guidelines [427] 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 [428]. It should be kept in mind that in LC 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.

7.10. In cirrhotic patients with malnutrition and muscle depletion, can PN ameliorate nutritional status, muscle mass, outcome, survival?

Recommendation 65

PN should be used in cirrhotic patients in whom oral and/or EN are ineffective or not feasible. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Commentary

The indication for PN in LC patients who cannot be fed orally or by EN is in keeping with recommendations in non-cirrhotic patients [4,5]. 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 LC, infused lipids are cleared from plasma and oxidized at rates similar to that in healthy individuals [55,56]. In infants and children fish oil containing emulsions appear to be associated with a lower risk of cholestasis and liver injury (see chapter 7). At present, there are no clinical outcome data showing a benefit of such emulsions in adult LC patients.

Regarding the composition of amino acid solutions, a standard solution can be used in patients with compensated LC. 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 LC patients with overt HE [429–431]. The efficacy of BCAA or BCAA-enriched solutions has been investigated in seven controlled but very heterogeneous trials [432–438], 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 [417,439]. It is important to reiterate that in LC patients, episodes of HE are precipitated by serious and life-threatening complications such as infection or hemorrhage, which are stronger determinants of survival than HE, and therefore it is not surprising that BCAA-based PN failed to improve short term survival. Recently, it has been demonstrated that, due to the absence of isoleucine from hemoglobin, blood is a protein source of low biologic value leading to BCAA antagonism after upper gastrointestinal hemorrhage [440]. This antagonism leads to hyperammonemia, but HE could potentially be overcome by the infusion of isoleucine alone [441]. Isoleucine solutions for i. v. infusions, however, are not commercially available. Special hepatic formula amino acid solutions (see above) contain high amounts of isoleucine in addition to other BCAAs, leucine and valine.

8. Transplantation and surgery

8.1. In patients with chronic liver disease/LC scheduled for surgery, when is preoperative nutrition therapy indicated/contraindicated compared to no preoperative nutrition therapy in order to a. achieve better survival, b. reduce complication rate?

Recommendation 66

LC 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. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 67

In the immediate preoperative period LC patients should be managed according to the ERAS approach in order to prevent unnecessary starvation.
Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary to recommendations 67 and 68

In malnourished LC patients, the risk of postoperative morbidity and mortality is increased after abdominal surgery [442,443]. Numerous descriptive studies have shown higher morbidity and mortality in LC patients with protein malnutrition when such patients undergo LT [25–27,31,116,444–446]. Recently, sarcopenia and frailty have been shown to carry an increased risk of morbidity and mortality on the waiting list and after transplantation [24,29,34,156,162–164,169–171,173,373,410]. Patients on the wait are at risk due to an inadequately low food intake [447] and those consuming a low protein diet (<0.8 $g \cdot kg^{-1} \cdot d^{-1}$) have an increased wait-list mortality [448]. Data from a pilot study suggest that preoperative nutrition support improves total body protein status and reduces postoperative infection rates [449] but there are no controlled trials showing that preoperative nutritional intervention improves clinical outcome.

Liver glycogen is depleted in LC 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 [42,43,217–219]. 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 two hours preoperatively, early feeding and mobilization [90,450,451].

8.2. Preoperatively in patients with chronic liver disease/cirrhosis, in which dosage should energy/protein by ONS and/or EN and/or PN be given in order to a. improve survival, b. decrease complication rate, c. maintain/improve nutritional status, d. shorten length of stay in ICU/hospital?

Recommendation 68

In LC patients scheduled for elective surgery nutrition management should proceed as recommended for cirrhosis.
Grade of recommendation GPP – Strong consensus (100% agreement)

Recommendation 69

Preoperatively, a total energy intake of 30-35 kcal × kg^{-1} × d^{-1} (126–147 kJ × kg^{-1} × d^{-1}) and a protein intake of 1.2-1.5 g × kg^{-1} × d^{-1} should be aimed for. These ranges cover recommended intakes depending on treatment goals, i.e. maintenance or improvement of nutritional status.

Grade of recommendation GPP – Strong consensus (100% agreement)

Recommendation 70

Obese patients can 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}.

Grade of recommendation GPP – Strong consensus (93% agreement)

Recommendation 71

In overweight/obese NASH patients scheduled for elective surgery nutrition management should proceed as recommended for NASH.

Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary to recommendations 68–71

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·m^{-2}) and severe obesity (BMI > 40 kg·m^{-2}) prior to liver transplantation are associated with increased mortality and morbidity [125,126,452,453]. Severe obesity prior to liver transplantation is associated with a higher prevalence of comorbidities (diabetes, hypertension), cryptogenic cirrhosis and increased mortality from infectious complications, cardiovascular disease and cancer [125,126]. 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" [125,454]. Some investigators found that severe obesity was associated with increased morbidity and mortality even when patients were classified according to "dry BMI" [125] while others found the amount of ascites and not BMI to increase mortality risk [454] or did not address this issue [126]. Also, in chronic liver disease obesity is an independent risk factor for worse clinical outcome [374,375].

8.3. Preoperatively in patients with chronic liver disease/cirrhosis, can specialized nutrition protocols when compared to no specialized nutrition protocols a. reduce postoperative mortality and morbidity, b. maintain or improve nutritional status?

8.3.1. Preoperatively in patients with chronic liver disease/cirrhosis, can special components (e.g. BCAA, omega-3 FA) of the nutrition solution when compared to a standard nutrition solution a. reduce postoperative mortality and morbidity, b. maintain or improve nutritional status?

Recommendation 72

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. (BM)

Grade of recommendation A – Strong consensus (100% agreement)

Recommendation 73

In children awaiting transplantation, BCAA-enriched formulas should be used in order to improve body cell mass. (BM)

Grade of recommendation B – Strong consensus (93% agreement)

Commentary to recommendations 72 and 73

Nutritional counselling plus ONS and nutritional counselling alone were equally effective in LC patients awaiting transplantation [384]. In a controlled randomized trial in LC 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 [199]. 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 [455]. Non-randomized studies by Kaido and colleagues showed fewer postoperative infections in transplanted patients who received preoperative BCAA-enriched ONS [456,457]. A retrospective analysis indicated reduced postoperative bacteremia in LT recipients receiving oral BCAA supplementation [458].

Pediatric transplant patients with predominantly cholestatic liver disease had improved body cell mass if they received BCAA-enriched formulas [459].

8.4. Postoperatively in patients with chronic liver disease/cirrhosis, when is nutritional therapy using – oral nutrition and/or EN and/or PN indicated/contraindicated when compared to no nutrition therapy in order to a. reduce mortality, b. reduce morbidity/co-morbidity, c. shorten length of stay in ICU/hospital?

Recommendation 74

After LT, normal food and/or EN should be initiated within 12-24 h postoperatively to reduce infection rate. (BM)

Grade of recommendation B – Strong consensus (100% agreement)

Recommendation 75

After scheduled surgery, chronic liver disease patients should be managed according to the ERAS protocol.

Grade of recommendation GPP – Strong consensus (100% agreement)

Recommendation 76

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. (BM)

Grade of recommendation B – Consensus (86% agreement)

Recommendation 77

PN should be used in patients with unprotected airways and HE when cough and swallow reflexes are compromised or EN is contraindicated or impracticable.

Grade of recommendation GPP – Strong consensus (100% agreement)

Recommendation 78

After the acute postoperative phase an energy intake of 30-35 kcal $\times$ kg^{-1} $\times$ d^{-1} (126–147 kJ $\times$ kg^{-1} $\times$ d^{-1}) and a protein intake of 1.2-1.5 g $\times$ kg^{-1} $\times$ d^{-1} should be aimed for.

Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary to recommendations 74–78

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 [460]. EN started as early as twelve hours after the operation is associated with a lower rate of infections than no artificial nutrition support [461]. In a direct comparison between PN and early EN, both strategies proved to be equally effective with regard to the maintenance of nutritional state [462]. Postoperatively there is a considerable nitrogen loss and patients remain in negative nitrogen balance for a prolonged period [91,93,199] necessitating an increase in the provision of protein or amino acids. Protein or amino acid intakes of 1.2–1.5 g $\times$ kg^{-1} $\times$ d^{-1} have been reported [91,460].

After non-transplant abdominal surgery LC patients have a reduced rate of complications and improved nitrogen economy if they receive nutritional support instead of just fluid and electrolytes [463,464]. EN (via jejunostomy) was associated with improved 7-day nitrogen balance compared with sequential PN/EN [464].

8.5. Postoperatively in patients with chronic liver disease/cirrhosis, can specialized nutrition protocols when compared to no such protocols a. reduce mortality, b. reduce morbidity, c. shorten length of stay in ICU/hospital, d. maintain or improve nutritional status, e. prevent sarcopenic obesity in long-term survivors after OLT?

Recommendation 79

For early EN nasogastric/nasojejunal tubes should be used as in non-liver disease surgery. (BM)

Grade of recommendation B – Strong consensus (100% agreement)

Commentary

Transplant patients who received early EN twelve hours after surgery developed fewer viral infections and had better nitrogen retention than those receiving no artificial nutrition support [461]. In comparison with PN, EN reduced complication rates and costs in transplant patients [462]. Whole protein formulas with [465–468] or without pre- and probiotics [461,462,469,470] or peptide-based formulas [471,472] have been used for early EN in adult liver transplant recipients. Formulae were administered via nasogastric or nasojejunal tubes [461,462,467,469] or via catheter jejunostomy [465,471,472] placed during laparotomy.

Long term survivors after liver transplantation are at considerable risk of becoming overweight or even obese and develop relevant morbidity due to metabolic syndrome [96,473,474]. More attention should be paid to approach the problem of sarcopenic obesity [97,98] by stringent postoperative physiotherapy and dietary counselling to overcome the deconditioning of pre-transplant chronic liver disease [99,101,102,105].

8.6. Postoperatively in patients with chronic liver disease/cirrhosis, can special components (e.g. BCAA, omega-3 FA) of the nutrition solution when compared to a standard nutrition solution a. reduce mortality, b. reduce morbidity, c. shorten length of stay in ICU/hospital, d. maintain or improve nutritional status, e. prevent sarcopenic obesity in long-term survivors after OLT?

Recommendation 80

After transplantation, enteral formula together with selected probiotics should be used to reduce infection rate. (BM)

Grade of recommendation B – Consensus (86% agreement)

Recommendation 81

BCAA-enriched formulas can be used in patients with HE in need of EN.

Grade of recommendation 0 – Majority agreement (79% agreement)

Commentary to recommendations 80 and 81

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 [467]. A recent meta-analysis [475] which included that study and two further randomized trials using a single *Lactobacillus* sp [466]. and two *Lactobacillus* spp. plus *Bifidobacterium* sp [465]. showed reduced infection rate with pre-and probiotics.

A recent meta-analysis [416] also showed that oral/enteral BCAA compared with isonitrogenous controls are beneficial for HE in LC. 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 LT has not been addressed in studies.

8.7. In adult organ donors, can specific nutrition regimens (e.g. glutamine, arginine) a. reduce/prevent ischemia/reperfusion injury, b. improve graft function, c. reduce postoperative mortality and morbidity?

Recommendation 82

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.

Grade of recommendation GPP – Strong consensus (100% agreement)

Commentary

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 [476]. 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.

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9. Nutrition associated liver injury (NALI)

9.1. In adults/children, can malnutrition cause liver injury associated with a. biochemical signs of hepatocyte lesion, b. impaired liver function, c. abnormal liver histology, d. chronic liver disease?

Statement 14

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.
Strong consensus (100% agreement)

Commentary

Severe malnutrition in children can cause fatty liver [477–479] which in general is fully reversible upon refeeding [478]. In children with kwashiorkor, there seems to be a maladaptation associated with less efficient breakdown of fat and oxidation of fatty acids [480,481] compared to children with marasmus. An impairment of fatty acid removal from the liver could not be observed [480]. Malnutrition impairs specific hepatic functions like phase-I xenobiotic metabolism [84,482,483], galactose elimination capacity [84] or plasma levels of C-reactive protein in infected children [484,485]. In nutritional intervention trials in cirrhotic patients, quantitative liver function tests improved more, or more rapidly in treatment groups. Measures of liver function included antipyrine [182,183] and aminopyrine [191] as well as galactose elimination capacity [182,183,195,486]. It is unknown, whether fatty liver of malnutrition can progress to chronic liver disease.

9.2. In adults/children, can overnutrition cause liver injury associated with a. biochemical signs of hepatocyte lesion, b. impaired liver function, c. abnormal liver histology, d. chronic liver disease?

Statement 15

Overnutrition can cause NAFLD or NASH which is a precursor condition for LC. Recommendations for the nutritional management of this condition are given in the section on NAFLD and NASH of these guidelines.
Strong consensus (100% agreement)

Commentary

The evidence available is reviewed in chapter 4 “NASH”.

9.3. In adults/children, can artificial nutrition (EN, PN) cause liver injury associated with a. biochemical signs of hepatocyte lesion, b. impaired liver function, c. abnormal liver histology, d. chronic liver disease?

Statement 16

In infants and children, PN can cause cholestasis, therefore named parenteral nutrition-associated cholestasis (PNAC) (BM)
Strong consensus (92% agreement)

Commentary

Due to the different features of PNAC in newborns and infants and parenteral nutrition associated liver disease (PNALD) in adults, PNAC is addressed as an exception in these guidelines on nutrition in adult liver patients.

Intestinal failure is the indication for long-term PN in many patients, particularly in infants and neonates and obviously, a clear distinction between intestinal failure vs. PN in the pathogenesis of ensuing liver injury is challenging in this population [487,488]. 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 recommendations 84 and 85). 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 [489]. Such 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 [487,490]. 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 [491]. This is reflected in the term PNAC that is frequently used in the pediatric literature for this condition [492], whereas the term PNALD has been used in both adult and pediatric patients [488,493,494]. In infants and neonates, mortality is high, up to 40 %, and PNAC has become a major indication for pediatric LT [492]. In adults, the incidence of advanced IFALD/PNALD ranges from 0 to 50 % and mortality ranges from 0 to 22 % [487]. Progressive IFALD/PNALD is an accepted indication for a timely lifesaving small bowel transplantation [495].

Statement 17

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. (BM).
Strong consensus (100% agreement)

Commentary

Cholestatic liver injury occurs in 50% of patients on long-term home PN [496]. In 1985, Bowyer and colleagues [497] described steatohepatitis in nine out of 60 patients on long-term PN. Liver injury persisted for a median of 15 months (8–95) and progressed to cirrhosis in three patients. Stanko and colleagues [489] 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 [487].

Grau and colleagues analyzed the association of liver disease and PN in 756 ICU patients on PN and/or EN [498]. They showed that the patients who developed liver injury had a characteristic profile in the way that they had a higher multiple organ dysfunction score on admission, they were septic, and they were treated with total PN.

In adults, IFALD/PNALD is related to female gender, age, length of time on PN, total caloric intake, and lipid or glucose overload [490,499]. 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 [487,490,493]. Both lack and excess of specific components of PN are being discussed as causal for PNALD. The fatty acid composition of lipid emulsions [496] as well as choline deficiency [500], and manganese toxicity

[490,493] have been linked to the occurrence of hepatic steatosis and cholestasis in adults and children.

9.4. In adults/children, can specialized nutrition protocols when compared to no such protocols improve/prevent a. biochemical signs of hepatocyte lesion, b. impaired liver function, c. abnormal liver histology, d. chronic liver disease?

Recommendation 83

In infants, children and adults, specialized nutrition protocols making optimal use of EN should be implemented. (BM)
Grade of recommendation B – Strong consensus (92% agreement)

Commentary

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 [501–505] and maximizing oral and enteral stimulation [502–505] and administering cyclic PN [502,503,506]. 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 [507]. In a multi-variate 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 [508]. A pilot study comparing standard (3.0 $g \cdot kg^{-1} \cdot d^{-1}$) vs reduced (1.0 $g \cdot kg^{-1} \cdot d^{-1}$) lipid dose showed a slower rise of cholestasis markers using reduced lipid doses [509]. The role of a limited lipid administration [510] is also strengthened by reports of a beneficial effect of a fish-oil emulsion given at 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ when compared to traditional soy bean emulsions infused at 1–4 $g \cdot kg^{-1} \cdot d^{-1}$ [511–517]. As a note of caution, the extent to which there is an overlap of cases reported in six separate publications of one group is unclear [512–515,518].

In a recent ESPGHAN position paper [519] early EN is recommended limiting i. v. lipid to 15–30 % of non-protein energy provided by PN and cyclic administration of PN once the patient is stable. The use of ursodeoxycholic acid (UDCA) and erythromycin has been reported to facilitate EN in premature infants on PN [520]. The authors of the ASPEN clinical guidelines analyzed seven publications on this issue and found a very low level of evidence for a beneficial role of UDCA in the treatment of PNAC [488]. They also analyzed the role of a multidisciplinary intestinal rehabilitation team in the management of IFALD and suggest to refer patients with PN-dependent intestinal failure to such a team conceding, however, a low level of evidence on this topic [488].

For the prevention of IFALD adults, the ESPEN guidelines [487] recommend infection control, maintenance of oral and/or enteral intake, cycled PN [521], avoidance of PN overfeeding and limiting the dose of soybean-oil based lipid to $\leq$ 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ [522].

9.5. In adults/children, can special components (e.g. omega-3 FA) of the nutrition solution when compared to a standard nutrition solution improve/prevent a. biochemical signs of hepatocyte lesion, b. impaired liver function, c. abnormal liver histology, d. chronic liver disease?

Recommendation 84

In case of PNAC in infants and children, lipid emulsions enriched with omega-3-fatty acids can be used. (BM)
Grade of recommendation 0 – Strong consensus (100% agreement)

Commentary

Lipid emulsions containing fish oils as the triglyceride source were proposed to be protective in PNALD. This has been evaluated in a number of publications including cases, case series, or cohort data. In these reports 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 [511–518,523,524]. 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% [525]. 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 [526]. 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 [505], or using lipid emulsions consisting of a mixture of either soy-bean based lipid and medium-chained triglyceride MCT-lipid [502,527], or a mixture of a fish-oil emulsion and a soy-bean olive-oil emulsion [528], or soy-bean based lipid and olive oil and MCT-lipid and fish-oil (SMOF emulsion) [527,529–533]. In randomized controlled trials comparing a SMOF 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 [529,531–533].

In an analysis of 292 infants receiving more than one day of PN postoperatively, 31 infants reached a serum bilirubin >100 μmol/L and 13 developed liver failure, whereas 86 (83%) reaching a serum bilirubin >33 μmol/L could be weaned off PN [534]. The authors question the routine use of a fish-oil emulsion in such a population outside of formal research protocols.

These results again bring into focus the uncertainty in the diagnosis of IFALD, PNALD and PNAC [487,488] because cholestasis alone is not necessarily equivalent to liver injury and in this view PNAC may be seen as a component of PNALD.

Both, the ASPEN guidelines paper on PNALD [488] and the ESPGHAN position paper on intestinal failure [519] conclude that currently there is no sound evidence favoring a specific lipid emulsion and that soy-bean based lipid infusion should be limited in hyper-bilirubinemia. Despite promising observations, the role of fish-oil emulsions needs to be established in randomized controlled trials. The authors of the ASPEN guideline delineate four questions to be answered [488]:

1. Will a long-term reduction in soy-based fat emulsion dose to $\leq$ 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ result in adequate growth and neurological development, and will essential fatty acid deficiency be prevented?
2. Is a fish-oil emulsion more effective than an equivalently dosed soy-based emulsion at preventing PNALD, promoting neurological development?
3. What is the incidence of essential fatty acid deficiency if the low dose is given over a long duration, and how should essential fatty acid deficiency be tracked in these individuals?
4. Is SMOF given at conventional lipid doses effective at preventing the development of PNALD while optimizing growth and development over the long term?

Recommendation 85

In adults with suspected PNALD, lipid emulsions with a reduced n6/n3 ratio can be used. (BM)

Grade of recommendation 0 – Strong consensus (92% agreement)

Commentary

In adults, less data is available regarding the effect of modifying quantity and/or composition of parenteral lipid on 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 [522]. The exchange of soy-bean based lipid by a 100 % fish-oil emulsion has been reported effective in two cases of PNALD [535,536]. In a series of 15 patients, the addition of a fish-oil emulsion to a soy-bean based lipid emulsion was associated with reversal of biopsy proven PNALD [537]. 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 [538]. Taken together, more data are needed before the routine use of fish-oil containing fat emulsions can be recommended for the treatment of PNALD [487].

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 Committee. 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 Committee. 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 Committee.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.022.

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