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Review Article

Diagnosis and treatment of nutritional deficiencies in alcoholic liver disease: Overview of available evidence and open issues

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ABSTRACT

Malnutrition is common in alcoholic liver disease and is associated with high rates of complications and mortality. In this article, the current literature was reviewed to highlight the relevance of proper nutritional management providing levels of evidence, when available. A PubMed search was performed for English-language publications from 1980 through 2014 with the keywords: alcoholic liver disease, nutritional deficiencies, nutritional support, enteral nutrition, parenteral nutrition, and protein–energy malnutrition. Manuscripts focused on nutritional approach in patients with alcoholic liver disease were selected.

Although nutritional support for malnourished patients improves the outcome of hospitalization, surgery, transplantation and reduces the complications of liver disease and the length of hospital stay, specific guidelines are scanty. Both enteral and parenteral nutrition appear to improve nutritional parameters and liver function; however data on survival is often conflicting. As micronutrient depletion is common in alcoholic liver disease and each deficiency produces specific sequelae, all cirrhotic patients should be screened at baseline for deficiencies of micronutrient and supplemented as needed.

In summary, protein–energy malnutrition and micronutrient depletion are clinical concerns in alcoholic liver disease. Nutritional therapy, including enteral nutrition, parenteral nutrition and micronutrient supplementation should be part of the multidisciplinary management of these patients.

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1. Introduction

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Western countries and represents a negatively relevant co-factor in the progression of chronic liver injury of different aetiology [1,2].

The term "ALD" includes a wide range of liver injury, including steatosis with or without fibrosis, alcoholic hepatitis (AH), cirrhosis and hepatocellular carcinoma, and represents one of the most common indications for liver transplantation (LT) in Europe and the United States [3].

Complete alcohol withdrawal represents the key treatment for ALD although possibly insufficient when facing with cirrhosis or severe AH [4]. Several medical approaches have been studied, but evidence about their effect on survival is still lacking [5].

Muscle wasting, weight loss, and nutritional deficiencies commonly occur in ALD, the underlying mechanisms including poor dietary intake (due to anorexia, altered sense of taste and smell, and nausea and vomiting), maldigestion and malabsorption (related to concomitant pancreatic insufficiency and bile acid deficiency, respectively), bacterial overgrowth due to reduced motility, loss of proteins secondary to portal hypertension, hypermetabolic state, insulin resistance, and impaired protein synthesis due to cytokine-induced inflammatory responses [6–8]. As malnutrition correlates with both higher rates of complications (variceal bleeding, ascites, encephalopathy, infections, and hepato-renal syndrome) and mortality, its finding in ALD may identify those patients at higher risk of hepatic decompensation and/or liver-related death [8], as clearly demonstrated by a recent study on 363 AH patients, reporting a one year mortality of 14% and 76% in those with mild or severe malnutrition, respectively [4]. Furthermore, malnutrition has also been associated with a longer stay in intensive care units, longer length of hospital stay, and higher mortality after LT [8].

Although no difference in the prevalence and severity of malnutrition has been observed between ALD and viral-related liver disease in one series [9]. Caly et al. reported a poorer nutritional

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Table 1
Grades of clinical recommendations based on literature studies strength.

Grade of recommendation	Evidence derived from
A	Meta-analysis of randomized controlled trials
B	At least one randomized controlled trial, one controlled study without randomization or one other type of quasi-experimental study
C	Comparative, correlation studies, or case-control studies
D	Expert committee reports or opinions or clinical experience of respected authorities, or both

status in patients with alcoholic cirrhosis compared to those with hepatitis C-related cirrhosis [10].

Nutrition plays an important role as supportive therapy, and the American Association for the Study of Liver Disease guidelines recommend that all ALD patients be screened for both protein–calorie deficiency and any specific micronutrient deficiencies (i.e. vitamin and mineral deficiency) [4].

Based on the above findings, the present review is aimed at addressing both the main patterns of malnutrition in ALD and the role of nutritional support in this specific setting, reporting the clinical recommendations with pertinent evidence-based strength (Centre for Evidence Based Medicine. Levels of Evidence. http://www.cebm.net/index.aspx?o¼1025, Table 1).

2. Methods

An extensive bibliographical search was performed in PubMed using the following keywords: alcoholic liver disease, nutritional deficiencies, nutritional support, enteral nutrition, parenteral nutrition and protein–energy malnutrition, in order to identify all the pertinent articles published between 1980 and 2014. The reference lists from the selected studies were manually examined to identify further relevant reports. Non-English language papers were excluded. The quality and strength levels of the results were considered and when available meta-analyses and systematic reviews, large epidemiological studies and randomized control trials represented the main source of data.

3. Results

A total of 82 articles with the strongest level of evidence specific to the scope of this review were identified.

3.1. Nutritional assessment

Nutritional assessment in ALD is based on detailed history and physical examination [8]. Of the several clinical markers of malnutrition of which none exclusive, the body mass index (BMI, kg/m^2) and the degree of weight loss are the most relevant ones, in spite of their potential unreliability in presence of fluid retention [8]. A more comprehensive assessment includes anthropometry and scoring systems such as the Nutrition Risk Screening, which considers the amount and duration of weight loss; the BMI for adults; percentile charts for children; the degree of appetite and the ability to eat and retain food (i.e. food intake) and 'stress factors', i.e. the effects of health status on nutritional requirements [8]. A further widely used tool, whose details are given in Table 2, is the Subjective Global Assessment (SGA), based on a standardized questionnaire aimed at assessing any changes in dietary intake, recent changes in body weight, gastrointestinal symptoms, functional capacity, and physical signs of malnutrition represented by loss of subcutaneous fat or muscle mass, oedema, ascites [8]. In addition, as listed in Table 3, several biochemical markers can help to better define malnutrition, even though albumin, prealbumin, and transferrin may lack accuracy as they are synthesized by the liver; a further critical point is the lack of correlation between these proteins and both the BMI and the lean body mass [8]. Moreover, the widespread use of albumin supplementation in cirrhotic patients can mask actual plasma albumin levels. The total lymphocyte count (TLC) has also been proposed as a useful indicator of nutritional status and outcome, even if its use in patients with hepatic disorders needs further evaluation as few pertinent studies are currently available [11]. Low insulin-like growth factor 1 levels may also be a marker of malnutrition [8], whilst serum creatinine may not accurately reflect the loss of muscle mass in patients with concomitant renal insufficiency. Noteworthy, in patients with chronic illnesses, including cirrhosis, muscle wasting can be assessed by measuring psoas muscle thickness by computed tomography (CT) scanning, a novel accurate, objective marker of nutritional status [8].

Table 2
Features of the subjective global assessment [8].

History
Weight change
Dietary intake change (relative to normal)
Gastrointestinal symptoms (that persisted for >2 weeks), including nausea, vomiting, diarrhoea, anorexia.
Functional capacity: full capacity, dysfunction (working suboptimally, ambulatory, bedridden).
Disease and its relation to nutritional requirements
Primary diagnosis (specify)
Metabolic demand (stress)
Physical (0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe)
Loss of subcutaneous fat (triceps, chest)
Muscle wasting (quadriceps, deltoids)
Ankle oedema
Sacral oedema
Ascites
SGA rating
A: Well nourished
B: Moderately (or suspected of being) malnourished
C: Severely malnourished

SGA, subjective global assessment.

Summary: As per current guidelines, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the bedside nutritional assessment using SGA and anthropometric measurements [12].

Grade of recommendation: C.

3.2. Protein–energy malnutrition

Malnutrition, characterized by an altered functional and structural development of an organism, results in an imbalance between the need, intake and utilization of nutrients and is usually associated with poor clinical outcomes.

Patients with chronic liver disease (CLD) are particularly prone to develop malnutrition due to the altered regulation by the affected liver of both the nutritional status and the energy balance. Moreover, the presence of CLD may also decrease the appetite, thus negatively influencing nutrient intake. As no difference

Table 3
Parameters aimed at assessing the presence and degree of malnutrition.

Parameters	Degree of malnutrition		
	Mild	Moderate	Severe
Albumin (g/dL)	3.5–3.0	2.9–2.5	<2.5
Transferrin (mg/dL)	200–150	149–100	<100
Pre-albumin (mg/dL)	22–28	17–10	<10
Retinol binding protein (mg/dL)	2.9–2.5	2.4–2.1	<2.1
Lymphocytes/mm^3	1500–1200	1199–800	<800

in malnutrition has been reported between alcoholic and non-alcohol-related liver diseases [9], the severity of liver damage per se is crucial in promoting nutritional disorders [6].

The prevalence of protein–calorie malnutrition in patients with ALD ranges from 20% to 60% in outpatients with alcoholic cirrhosis to the almost 100% in hospitalized patients with AH [6,13,14]. ALD represents a strong predictor of malnutrition due to the several risk factors associated with chronic alcohol abuse [11] and protein–calorie malnutrition may in turn promote complications, e.g. encephalopathy and/or bacterial infections in ALD patients [15]. Moreover, malnutrition may itself have a negative impact on liver integrity as reported several decades ago in malnourished children with kwashiorkor [16]. The current lack of strong clinical practice guidelines aimed at assessing and grading ALD-related malnutrition accounts for the poor recognition, diagnosis and treatment of this condition. Accordingly, physicians should be trained to this specific field as nutritional supplementation can be effective in improving liver function and is also positively affecting survival as suggested by short-term follow-up studies [17–19]. Conversely, a recent Cochrane meta-analysis failed to confirm a clear-cut benefit on morbidity or mortality from the oral, enteral or parenteral nutritional support even when specific nutrient deficiencies have been identified and corrected [7].

Summary: Although several studies have recommended nutritional supplementation for ALD malnourished patients, the available results are often inconclusive and further studies are needed to clearly define the role of nutritional support.

Grade of recommendation: C.

3.3. Micronutrient depletion

The depletion of fat-soluble and water-soluble vitamins or various minerals is common in patients with ALD, each deficiency producing specific symptoms, signs, and complications [6,20]. The ESPEN suggests a baseline screening of all cirrhotics for possible deficiency of serum zinc, calcium and vitamins leading to their supplementation whenever needed [21] and an annual check-up once stable levels are achieved.

The mechanisms underlying micronutrient deficiency include dietary restrictions, frequent paracentesis, diuretic regimens and lactulose therapy. Advanced liver disease associated with cholestasis, bacterial overgrowth and/or malabsorption, causes severe deficiencies of fat-soluble vitamins and other nutrients [22].

Summary: Baseline screening for micronutrient depletion and an appropriate correction when necessary are recommended.

Grade of recommendation: D.

3.3.1. Folate deficiency

Folate deficiency typically characterizes ALD due to reduced dietary folate intake, intestinal malabsorption, reduced liver uptake and storage, and increased urinary excretion [23]. Herbert et al. originally reported that 80% of the 70 chronic alcoholics admitted to a large US urban hospital showed low serum folate levels, with severe deficiency in 44% of them [24].

Both dietary and endogenous folate are involved in the hepatic methionine metabolism, which regulates homocysteine levels, antioxidant defences, DNA assembly, lipid export, and all epigenetic methylation reactions contributing to the gene expression regulation [23]. Dietary folates are metabolized in the liver and other tissues and the final metabolite is S-adenosylmethionine (SAM), which acts as a methyl donor for all the methylation reactions involving DNA, histones, and proteins [23].

The methionine metabolic pathways are deeply influenced by alcohol consumption and folate deficiency may promote liver disease resulting in defective DNA synthesis and stability, both associated with an increased risk for hepatocellular carcinoma [25] and reduced methylation capacity on the expression of genes related to liver injury [26].

The beneficial effect of both methyl donor SAM and betaine as protective against the development of experimental ALD in animal models has been clearly shown [27,28], whilst inconclusive results have been achieved in the clinical trials focused on the efficacy of SAM in established ALD [29–31].

Summary: Even though folate should be properly supplemented in ALD patients, inconclusive results are available regarding the therapeutic effect of its final metabolite (SAM).

Grade of recommendation: C.

3.3.2. Water-soluble vitamin deficiency

Due to the hepatic activation and transport of vitamins B_1, B_6 and others, water-soluble vitamin deficiency commonly occurs in liver disease.

Thiamine (vitamin B_1) deficiency is a well-recognized complication of ALD leading to Wernicke's encephalopathy and Korsakoff's syndrome [20].

As cyanocobalamin (B_{12}) deficiency has been reported in CLD, serum cobalamin levels determination has been suggested; however, falsely elevated B_{12} levels have been reported in ALD due to the inclusion of endogenous metabolically inactive forms of cobalamin. Accordingly, holotranscobalamin, i.e. the active form of cobalamin, has been reported to be more reliable as an early marker of vitamin B_{12} deficit in alcoholics [32].

Summary: Vitamin B1 and/or B12 deficiency should be promptly treated to avoid complications (i.e. Wernicke's encephalopathy, Korsakoff's syndrome, megaloblastic anaemia, neuropathies).

Grade of recommendation: C.

3.3.3. Fat-soluble vitamin deficiency

Decreased bile acid production, decreased oral intake, derangement in hepatic synthesis of carrier proteins, and other mechanisms can all account for the deficiency of fat-soluble vitamins (i.e., A, D, E, and K) in CLD patients [20].

Vitamin A deficit with loss of night vision, nyctalopia and more rarely xerophtalmia, has been reported in alcoholics [33]. Alcohol intake has a profound impact on the whole body's retinoid homeostasis, but the effects of chronic alcohol consumption are tissue specific; in other words, alcohol consumption is associated with a decrease in the hepatic retinoid content, while extra-hepatic retinoid levels are elevated [34]. Noteworthy, caution in replacing vitamin A levels is mandatory as continuous alcohol intake stimulates cytochrome P450 with the conversion of retinoids into toxic metabolites [35].

Vitamin D deficiency has already been reported in ALD, especially in the presence of established cirrhosis [36]. In a recent European study on 324 ALD patients, low 25(OH) vitamin D levels were associated with increased liver damage and mortality, suggesting that vitamin D might be both a biomarker of severity and a potential therapeutic target in ALD [37]. Notably, a recent Danish study suggested that a single oral mega-dose (300,000 IU) of cholecalciferol was more effective than ergocalciferol in the treatment of vitamin D deficiency [38], although these results need to be reproduced in larger cohorts of ALD patients.

Vitamin E exerts definite antioxidant effects. However, whilst several studies have suggested a link between vitamin E deficiency and progression from NAFLD to non-alcoholic steato-hepatitis (NASH) [39], comparable data in ALD are still scanty.

Vitamin K is a known co-factor for the carboxylation of multiple proteins, including blood coagulation factors and its deficiency, common in advanced liver disease, is usually responsible for bleeding. Despite the lack of specific studies addressing the vitamin K status in ALD patients, those with impaired prothrombin time

and/or international normalized ratio (INR) should receive vitamin K supplementation [20].

Summary: Supplementation with fat-soluble vitamins is not routinely recommended for ALD patients, except for vitamin D deficiency, which should be corrected in all patients with advanced CLD [36].

Grade of recommendation: B.

3.3.4. Other nutritional deficiencies

A deficit of other micronutrients including ascorbic acid, magnesium and zinc, has also been observed in ALD patients, but the need for their supplementation remains a matter of debate.

Although full-blown vitamin C deficiency is currently uncommon in Western countries, sporadic cases of scurvy have been described in malnourished patients including alcoholics [40,41]. That prompts for careful skin examination and ascorbic acid measurements when available in this setting [41].

Zinc or magnesium deficiency can provoke dysgeusia or altered taste sensation, partially explaining the decreased dietary intake reported in most CLD patients [20]. Zinc deficiency, common in liver disease especially in ALD, may be partially due to decreased intake, increased losses secondary to malabsorption, increased dietary requirement and, possibly, a diuretic regimen [22,42]. The complications of zinc deficiency include skin lesions, impaired night vision, altered taste and smell, immune dysfunction, hypogonadism, encephalopathy, altered protein metabolism and retarded wound healing [42]. The severity of zinc deficiency parallels the extent of liver damage as suggested by lower serum zinc levels in alcoholic cirrhotics vs. non-cirrhotics, both groups showing a significant decrease of serum zinc levels when compared to healthy controls [43]. According to some studies, zinc supplementation can revert the known manifestations of zinc deficiency in ALD [44], even if the results remain inconclusive. In the series by Zarski *et al.* zinc sulfate was given at a dosage of 600 mg/daily for 10 days to ALD patients and for 10, 30, and 60 days to alcoholic cirrhotics; both groups normalized serum zinc levels without adverse reactions, although some cirrhotics maintained persistently low levels [45]. Bianchi and colleagues administered a long-term oral zinc supplementation (200 mg tid for 2–3 months) to cirrhotic patients, including alcoholics, with beneficial effects on both the liver metabolic function and nutrition parameters [46]. Since nutritional parameters remained below lower limits of normal, further studies are needed on both the interaction between zinc and ALD and the long-term outcome of oral zinc supplementation, to define the optimal duration and overall dose.

Magnesium deficiency affects patient's appetite, and its levels have been shown to be an independent predictor of muscle strength [47]. The mechanisms underlying magnesium deficiency are still far from being fully understood as its deficit may be due to cirrhosis or heavy alcohol intake as well. Additionally, the need for magnesium supplementation is still controversial [47].

Other minerals, such as selenium, may decrease with liver disease but the effects are poorly known in cirrhotic patients [20].

Summary: Guidelines for assessing micronutrient deficiency in ALD patients are scanty and evidence supporting their supplementation is still inconclusive. Moreover, the potential benefits and the possible harmful effects of any dietary supplementation should be considered.

Grade of recommendation: D.

3.4. Nutritional therapeutic approaches

3.4.1. Dietary interventions

Dietary interventions represent a relevant step in the management of patients with ALD to reduce the length of hospital stay, to improve the outcome of surgery and transplantation and to reduce the rate of complications [8].

Table 4
Summary of general nutrition guidelines for patients with cirrhosis, released by the European Society for Clinical Nutrition and Metabolism.

Intervention
Overall provision 30–35 kcal/kg dry body weight
Calories distribution (%):
– Carbohydrates 50–60
– Proteins 25–30 (1–1.5 g/kg body weight)
– Fats 15–20
Avoidance of unnecessary dietary restriction
A low-sodium diet (<2 g/day) should be recommended only if ascites or oedema is present
Frequent (4–6) small meals including night-time snacks: to be encouraged
Screen for deficiency of serum zinc, calcium and vitamins A, D, E and K and supplement as needed
Protein restriction for acute hepatic encephalopathy
In case of protein intolerance: vegetable or dairy and branched chain amino acids

Nutritional management should firstly be addressed to cover basal needs and then to provide additional sources for the hypermetabolic state. Caloric need estimation for ALD patients, based on the Harris-Benedict equation, may be inaccurate owing to an underestimate of the caloric needs by even 15–18% when compared with the measurement using indirect calorimetry [8]. General nutritional guidelines for patients with cirrhosis as released by the ESPEN are listed in Table 4 [48]. Unnecessary dietary restrictions should be avoided in order to reduce the risk of malnutrition or micronutrient deficiency and a low-sodium diet should be only recommended in decompensated cirrhosis with ascites and oedema. Due to the limited reserves and inability of the liver to handle prolonged starvation due to reduced gluconeogenesis, patients with cirrhosis are recommended to assume frequent meals, including nighttime snacks [49]. In this context, a randomized controlled trial (RCT) reported an increase of the total body protein stores, with a sustained gain of 2 kg over a 12-month period, in patients receiving a nighttime snack when compared with patients receiving an equicaloric diet but lacking the late evening meal [49]. Additionally, cirrhotic patients fasting for more than 12 hours should receive intravenous glucose at the rate of endogenous hepatic glucose production (2–3 mg/kg/d). Protein restriction should be limited to patients with acute hepatic failure, whilst such restriction is not required in the medium or long-term management of patients with liver disease as this limitation may be responsible for an increased incidence of complications related to malnutrition [50]. In a recent RCT 30 cirrhotic patients hospitalized for an episode of encephalopathy received a 14-day low-protein regimen with progressive increments or a normal protein diet, in addition to the standard measures to treat hepatic encephalopathy. Overall, the protein intake of 1.2 g/kg/day prevented muscle catabolism without the concomitant precipitation of hepatic encephalopathy [51]. The ESPEN consensus guidelines recommend that the daily protein intake in patients with liver disease should possibly be from 1.0 to 1.5 g/kg depending on the degree of hepatic decompensation [52,53].

Cholesterol intake should be limited, as high cholesterol levels have been reported to increase the degree of liver fibrosis [54], the risk of cirrhosis and liver cancer [55] and to suppress the immune function [56]. The use of statins should be encouraged in cirrhotic patients with hypercholesterolemia [57].

Branched-chain amino acids (BCAAs) have nutritional and/or metabolic effects on the liver, muscles, and brain, but their levels are reduced in cirrhosis. There is evidence that long-term oral BCAA supplementation (about 0.25 g/kg) both exerts nutritional benefits and reduces the recurrence rates or symptoms of hepatic encephalopathy in patients with cirrhosis [59]. However, the

currently available studies are often controversial [58]: an initial RCT including 37 cirrhotic patients reported that BCAA supplementation was superior to conventional protein supplements in improving hepatic encephalopathy [59], whilst two other RCTs failed to confirm these findings [60,61], even if they had a small sample size (eight and four patients only, respectively) and the BCAAs regimen was short-term (11–12 days). More recently, two RCTs including larger cohorts (174 and 646 patients, respectively) focused on the long-term use of BCAAs (1–2 years) among patients with alcoholic cirrhosis; both studies reported a decreased morbidity and mortality and an improved quality of life in the group receiving BCAAs [62,63]. According to available data, BCAA supplementation should be recommended in ALD patients with hepatic encephalopathy. BCAA-enriched formulae are available for patients with hepatic encephalopathy who require enteral nutrition (EN) by a nasogastric tube.

Summary: ALD patients should avoid unnecessary dietary restrictions. Cirrhotic patients should receive a daily protein intake of approximately 1.0–1.5 g/kg and should have frequent meals including night-time snacks. Intravenous glucose should be administered to cirrhotic patients fasting for more than 12 hours; BCAA supplementation should be performed in ALD patients with hepatic encephalopathy.

Grade of recommendation: B.

3.4.2. Enteral nutrition (EN)

In ALD patients unable to meet their caloric requirements through normal feeding, supplementary EN ensures the adequate energy and protein intake without the risk of complications including hepatic encephalopathy [12].

EN is largely preferred over parenteral nutrition (PN) due to the lower incidence of serious complications and far lower costs. Moreover, the presence of luminal nutrients represents an important trophic factor for intestinal mucosa, which may prevent bacterial translocation and maintain gastrointestinal functions.

Whole protein formulae are generally recommended and more concentrated high-energy formulae are preferable in patients with ascites to avoid fluid unbalance. BCAA-enriched formulae should be administered to patients with encephalopathy [12]. The oral route is preferable; however, in the case of inadequate oral intake due to the disease severity, tube feeding is recommended, even in patients with oesophageal varices who can safely undergo the procedure without any risk of variceal haemorrhage [64]. On the other hand, percutaneous endoscopic gastrostomy (PEG) should be avoided in the presence of ascites and coagulopathy [65].

Five RCTs have shown an improvement both in nutritional status and liver function with EN in patients with AH [17,66–69], but data on the long-term survival are often inconclusive as limited to a small samples or derived from a short-term follow-up. Noteworthy, Cabré et al. enrolled 71 patients with severe AH randomized to receive 40 mg/day prednisolone ($n = 36$) or enteral tube feeding (2000 kcal/day) for 28 days ($n = 35$) and followed for one year or until death. Eventually, EN was comparable to steroids in the short-term, although death occurred earlier with EN. Steroid therapy however was associated with a higher mortality rate in the immediate weeks after treatment, mainly because of infections [17]. Similar results have been reported in a series including 273 male patients and comparing oxandrolone plus enteral feeding vs. placebo in severe AH. Combined treatment obtained a lower mortality at six months in the subset of patients with moderate malnutrition [68], supporting the preference for early EN to be maintained for a sufficient period.

Four RCTs comparing EN with a standard diet in alcoholic cirrhotics have shown the improvement in nutritional parameters and liver function with EN; however, the data on survival was conflicting, due to the heterogeneity in both the sample size and the inclusion/exclusion criteria [70–73]. In particular, in the trials by Cabré et al. and Kearns et al. [71,73] the results are difficult to interpret due to the large number of patients with AH, which is known to benefit from EN [17] and the low number of patients included in the first series [71].

In a recent multicentre prospective RCT including 99 alcoholic cirrhotics with jaundice but without AH, patients were randomized to receive either conventional symptomatic treatment alone ($n = 55$) or in association with EN with a supply of 35 kcal/kg/day for four weeks, followed by an oral nutritional support alone lasting two months ($n = 44$) [74]. Disappointingly, EN failed to improve survival and hepatic or nutritional parameters, even if results could have been partially influenced by the inclusion of Child–Pugh C cirrhotic patients with ascites, suggesting the use of EN in earlier stages of ALD.

Summary: EN is preferable over PN whenever feasible and is associated with improvement in nutritional status and liver function in ALD patients, even if data on long-term survival are often inconclusive.

Grade of recommendation: A.

3.4.3. Parenteral nutrition (PN)

EN has been reported to be as effective as PN, though with lower costs and fewer side effects, therefore the current indication for PN support is restricted to a small group of ALD patients for whom enteral feeding has failed or is contraindicated, or when patients need to stay fasting for 72 h or more [48].

PN should be started early in ALD patients with moderate or severe malnutrition, who cannot be sufficiently fed either orally or enterally [48]. PN should be administered via a central catheter, carefully considering the increased risk of several complications such as sepsis, venous thrombosis, pneumothorax, and lymphatic duct damage. In patients with long-lasting and severe malnutrition, an extremely cautious introduction of PN and careful patient monitoring for the risk of re-feeding syndrome are of paramount relevance.

In 1980 a RCT by Nasrallah et al. [75] reported an improved survival in 18 AH patients receiving parenteral supplementation of 70–85 g of amino acids in addition to a standard diet (3000 kcal/day and protein 100 g/day) when compared to 17 similar cases on standard diet alone. Unfortunately, six further studies failed to confirm the above promising results [76–81], probably due to the different inclusion criteria, as the study by Nasrallah et al. included mild to moderate AH. Notably, an improvement in nutritional status and nitrogen balance was reported in all these studies. In particular, in a RCT from Simon et al., 12 patients with moderate and 22 with severe AH were randomized for a four-week regimen of peripheral PN or standard therapy; comparable results were found in moderate AH, but with a more rapid improvement in liver tests, particularly bilirubin levels in severe alcoholic hepatitis, without deleterious effects on encephalopathy or ascites [79].

The role of PN in alcoholic cirrhotics has been reported in only one series in which 40 in-patients with total serum bilirubin greater than or equal to 5 mg/dl were randomized to receive an oral diet containing 40 kcal per kg per day alone or in combination with parenteral supplementation (40 kcal/kg/day and 200 mg nitrogen/kg/day using a central catheter). Despite an improvement in bilirubin and nutritional status in the PN subset, overall survival did not improve and was comparable in both groups (5%) [77].

Summary: PN should be limited to a small group of ALD patients for whom enteral feeding has failed or is contraindicated or when patients need to stay fasting for at least 72 hours. PN showed promising results in terms of improvement in the nutritional status of ALD patients, however data on survival are inconclusive.

Grade of recommendation: A.

Table 5
Summary of current evidence about nutritional supplementation in alcoholic liver disease patients.

Key points
Alcoholic liver disease patients are at high risk for malnutrition and when malnourished can develop complications negatively affecting both the clinical outcome and healthcare costs.
The European Society for Clinical Nutrition and Metabolism recommends the bedside nutritional assessment using Subjective Global Assessment and anthropometric measurements.
Further studies are needed to clearly define the role of nutrient supplementation in alcoholic liver disease patients.
Alcoholic liver disease patients should be screened at baseline for micronutrient depletion and properly supplemented when necessary.
Folate, vitamin B1 and B12 deficiency should be promptly treated to avoid complications. Inconclusive results are currently available regarding the therapeutic effect of folate's final metabolite.
Vitamin D deficiency should be treated and corrected.
The actual need for supplementation of micronutrients including ascorbic acid, zinc, selenium and magnesium in alcoholic liver disease patients remains to be determined.
Unnecessary dietary restrictions should be avoided and appropriate dietary intake should be given according to European Society for Clinical Nutrition and Metabolism recommendations.
Both enteral (first choice whenever possible), and parenteral nutrition seem to improve the nutritional parameters and liver function. However, their effect on survival remains to be proven.

4. Conclusion

Patients with ALD are at high risk for malnutrition, which in turn carries a high risk of developing complications, negatively affecting clinical outcome and increasing healthcare costs. Thus, physicians should detect, diagnose and treat nutritional deficiencies early in this subset of patients. The baseline evaluation of a patient's nutritional status by SGA and anthropometric measurements is recommended by the ESPEN. Nutritional support for malnourished ALD patients is aimed at improving the outcome of hospitalization, surgical procedures, and transplantation and at reducing the length of hospital stay and the rate of complications. Nevertheless, there is still no approved therapy for this common and often devastating disease. Both EN, the first choice whenever possible, and PN seem to improve nutritional parameters and liver function in ALD patients, but fail in increasing overall survival. Micronutrient depletion is common in ALD patients and each deficiency produces specific sequelae. According to the ESPEN guidelines, all cirrhotic patients should be screened at baseline for deficiencies of micronutrients and then properly supplemented. Summary of current evidence on nutritional supplementation in ALD patients is reported in Table 5.

A complete nutritional assessment, evaluation for EN, PN and micronutrient supplementation supports the need for a multidisciplinary management of ALD patients.

Conflict of interest
None declared.

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