Malnutrition and Nutritional Support in Alcoholic Liver Disease: a Review

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Abstract

Malnutrition is associated with alcoholic liver disease (ALD) and related complications such as hepatic encephalopathy and increased rate of infections. Avoidance of prolonged fasting and overly restrictive diets is important to avoid poor nutrition. Adequate intake of calories, protein, and micronutrients via frequent small meals and evening supplements and/or enteral and parenteral nutrition when indicated has been associated with reduced mortality and morbidity in patients with ALD. Modification of protein/fat sources and composition in addition to probiotic supplementation are promising interventions for decreased progression of ALD and its complications.

Keywords

Alcoholic liver disease
Diet
Nutrition
Enteral nutrition
Parenteral nutrition

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Introduction

Alcoholic liver disease (ALD) includes a range of injury that encompasses steatosis, alcoholic hepatitis, and cirrhosis due to chronic ethanol ingestion and has been associated with poor nutritional status [1]. Alcohol consumption can lead to hepatotoxicity, both resulting in and possibly enhanced by malnutrition [2]. It has also been demonstrated that in patients with liver disease, reinforcement of adequate nutrition by physicians and other members of the healthcare
team is associated with improved survival and quality of life when compared to nutritional counseling alone [3].

Current guidelines from the American Association for the Study of Liver Disease (AASLD) recommend frequent interval feedings for patients with ALD with an emphasis on nighttime snacks and morning feeding (1.2–1.5 g/kg for protein and 35–40 kcal/kg for energy) to improve nitrogen balance. In addition, assessment for vitamin and mineral deficiencies and repletion are recommended [4]. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends not only optimizing oral intake of food but also supplementation with oral nutritional supplements or tube feeding in patients unable to maintain adequate intake [5]. A recent meta-analysis supports these practice guidelines with pooled data from 13 randomized controlled trials suggesting that nutritional therapy in patients with ALD reduces mortality and complications such as encephalopathy and infections [6••].

However, there continues to be a need for ongoing study to evaluate the effects and means of nutritional support in ALD. A Cochrane meta-analysis failed to demonstrate clear morbidity and mortality benefits from either oral, enteral, or parenteral nutritional support in part due to the large number of screened studies excluded from final analysis. A review of the characteristics of excluded studies reveals many of the challenges in evaluating the role of nutrition and nutritional support in ALD. There is wide variation in supplement formulation, protocols for nutritional support, methodology for evaluation/monitoring of nutritional status, and frequent lack of adequate untreated controls [7]. Another meta-analysis evaluating 6 trials and including 470 patients with cirrhosis from all causes revealed no overall difference in mortality between patients who received oral or enteral nutritional supplementation in comparison to those that did not. However, subgroup analysis of three of the four studies with oral supplementation did demonstrate a reduction in mortality in patients receiving oral nutritional supplements [8]. Therefore, current evidence suggests that oro-enteral nutritional supplementation can lead to decreased complications and mortality in patients with ALD [8, 9].
Consistent intake of alcohol may reach up to 500 kcal/day in some consumers. Alcohol can account for up to one third of total caloric intake for many social drinkers. In alcoholics with liver disease, ethanol consumption can account for as much as half of their daily total calorie intake [10].

Protein calorie malnutrition is common in alcoholics with and without ALD. In the Veterans Administration Cooperative Study on Alcoholic Hepatitis, 363 patients with alcoholic hepatitis were enrolled between hospital days 5 and 10 at six Veterans Administration medical centers [11]. Complete nutritional assessments were performed that included dietary recall histories, estimates of energy requirements, and nitrogen balance/protein utilization in addition to measurements of triceps skinfold thickness and arm muscle circumference. Serum protein, albumin, and transferrin levels and decreased lean body mass (estimated by creatinine-height index) and evaluation of cellular immune function (measured by total lymphocyte count and response to skin anergy testing) were also evaluated. Every patient with alcoholic hepatitis or cirrhosis had malnutrition of varying severity. In alcoholic subjects without liver disease, protein calorie malnutrition was observed in 62 % of cases. Patients with compensated alcoholic cirrhosis that abstain from alcohol without concomitant alcoholic hepatitis also often have protein calorie malnutrition [12].

In addition, malnutrition from ALD may in turn increase hepatocyte susceptibility to alcohol toxicity [2, 13]. Increasing severity of malnutrition in patients with ALD has been associated with increased mortality, approaching 80 % in patients with severe protein calorie malnutrition. These observed differences in mortality among patients with moderate versus severe protein calorie malnutrition have been seen to persist over 30 days and increase over a 6-month period of observation [11].

For patients with ALD that are selected for transplantation, it is unclear how nutritional status prior to transplantation impacts post-transplant outcomes. While no individual measure of nutritional status at the time of listing or transplantation has been correlated with post-transplant graft and patient survival, poor pre-transplant nutritional status has been
associated with increased post-transplant ICU and total length of stay, ventilator support, and rate of infections [14, 15, 16, 17].

There are many potential mechanisms for malnutrition associated with ALD. Poor dietary intake from anorexia due to early satiety in the setting of elevated tumor necrosis factor, altered sense of taste and smell, or resultant nausea and vomiting play a role [12, 18, 19]. Alcohol substitution is also common, with an increasing contribution of ethanol as a fraction of total consumed calories in heavy drinkers [20]. If admitted to hospital, patients may be kept without oral intake for procedures or other diagnostic testing. Complications associated with ALD such as gastrointestinal hemorrhage or pancreatitis may also limit adequate oral intake. Furthermore, patients with consequences of portal hypertension may be placed on dietary restrictions that limit sodium and fluid intake that may not be appealing or consistent with patient preferences [12].

Malabsorption from pancreatic insufficiency in patients with chronic pancreatitis can contribute as can malabsorption from bile acid deficiency [21, 22, 23, 24]. In addition, there can be direct ethanol impairment of absorption of nutrients [25, 26]. Medications often used to manage patients with liver disease such as lactulose and antimicrobials may be associated with nutrient loss through increased gastrointestinal transit and stool output. Inflammatory cytokines may also lead to reduced gastrointestinal motility, which can contribute to malabsorption of nutrients if small bowel bacterial overgrowth develops [20].

Finally, advanced liver disease can result in a hypermetabolic and catabolic state that can contribute to and exacerbate poor nutritional status [27, 28, 29]. Systemic inflammation in alcoholic hepatitis or in end-stage liver disease from alcohol can lead to catabolic protein breakdown and impaired protein synthesis [27, 30].

**Assessment of Nutritional Status**

Nutritional assessment to identify modifiable nutritional risks associated with increased morbidity and mortality plays an integral role in the management of patients with ALD. The AASLD guidelines
recommend that these patients should be screened for both protein-calorie deficiency and specific micronutrient deficiencies including vitamin and mineral deficiencies [4].

However, assessing nutritional status can be difficult in this population due to abnormalities in fluid homeostasis and compartmentalization, protein metabolism, and bone modeling and mineralization [31].

History and Physical

A detailed history and physical exam are important and inexpensive tools to assess nutritional status in ALD. Subjective evaluation includes obtaining a history on body weight, appetite change, dietary and alcohol intake, duration and frequency of gastrointestinal symptoms, and functional status. However, weight change can be unreliable as ALD patients frequently have sodium and water retention. An objective evaluation would include measurement of subcutaneous fat loss, muscle wasting, peripheral edema, ascites, and clinical findings associated with micronutrient deficiencies (Table 1) [32]. The Subjective Global Assessment (SGA) is a commonly used multiparameter assessment tool utilizing a focused history and physical exam (Table 2). This tool can provide a method for clinicians to combine nutritional risk parameters for nutritional ranking: (1) well nourished, (2) moderate or suspected malnutrition, or (3) severe malnutrition. A drawback of the SGA is that it requires the clinician to make his or her own judgment with no concrete scoring for a final numerical rating [1, 33].

Table 1

Clinical exam for micronutrient deficiencies in alcoholic liver disease patients

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (retinol)</td>
<td>Night blindness, increased fibrosis</td>
</tr>
<tr>
<td>E</td>
<td>Skin changes</td>
</tr>
<tr>
<td>D</td>
<td>Osteopenia and osteoporosis</td>
</tr>
<tr>
<td>B1 (thiamine)</td>
<td>Wernicke encephalopathy, neuropathy, beriberi with high output heart failure</td>
</tr>
<tr>
<td>B3 (niacin)</td>
<td>Pellagra (dementia, diarrhea, and dermatitis)</td>
</tr>
</tbody>
</table>

From [32]
B₆ (pyridoxine)  Neuropathy, sideroblastic anemia, elevated AST/ALT ratio
B₉ (folate)  Megaloblastic anemia

B₁₂ (cyanocobalamin)  Megaloblastic anemia, subacute combined degeneration, neuropathy
C (ascorbic acid)  Scurvy

Minerals  Clinical Findings
Iron  Anemia
Calcium  Osteopenia and osteoporosis
Magnesium  Cardiomyopathy
Phosphorous  Cardiac arrhythmias, delirium tremens
Selenium  Cardiomyopathy
Zinc  Ageusia and skin changes

From [32]

Table 2
Subjective Global Assessment (SGA) assessment tool

<table>
<thead>
<tr>
<th>History</th>
<th>Physical exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight change</td>
<td>1. Loss of subcutaneous fat in triceps and chest</td>
</tr>
<tr>
<td>2. Dietary intake change</td>
<td>2. Muscle wasting in deltoids and quadriceps</td>
</tr>
<tr>
<td>3. Gastrointestinal symptoms (persisting for more than 2 weeks):</td>
<td>3. Ankle edema</td>
</tr>
<tr>
<td>Nausea</td>
<td>4. Sacral edema</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5. Ascites</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 = normal</td>
</tr>
<tr>
<td>4. Functional status</td>
<td>1+ = mild</td>
</tr>
<tr>
<td>5. Evaluation of individual nutritional requirements</td>
<td>2+ = moderate</td>
</tr>
<tr>
<td>6. Note the primary diagnosis and evaluate the presence of metabolic stress (none, low, moderate, or high)</td>
<td>3+ = severe</td>
</tr>
</tbody>
</table>

SGA Rating:
A = well nourished
B = moderately malnourished
C = severely malnourished

From [1, 33]

Laboratory Tests
The liver is an important site of protein synthesis and deficiencies in serum albumin, pre-albumin, transferrin, and clotting factors that can suggest malnutrition and/or hepatic synthetic dysfunction. The average adult liver synthesizes about 15 g of albumin per day [34]. Hypoalbuminemia is common in cirrhosis, and a fall in albumin concentration may suggest liver dysfunction and reduced synthesis [34]. Abnormal prothrombin time and international normalized ratio (INR) may also reflect functional liver impairment in patients with ALD. Therefore, it is important to check for plasma levels of vitamin A, D, and E and consider empiric supplementation of vitamin K in the setting of elevated INR. Patients with anemia should also have iron studies and measurement of serum folate and vitamin B12 levels.

Ancillary Tests

Anthropometry is a rapid, inexpensive, and noninvasive bedside tool used to assess body fat and lean tissue stores. It is considered one of the most useful tests for indirectly estimating body composition and assessing nutritional status in cirrhotic patients [35]. However, ascites and edema can contribute to body weight and inflated body-mass index (BMI) values, and anthropometry may therefore underestimate malnutrition in cirrhotic patients [36]. Skinfold thickness and body circumference measurements are less affected by water retention than BMI. Mid-arm muscle circumference (MAMC) is used to assess lean tissue stores and triceps skinfold thickness (SFT) is used to measure fat reserves. Values less than the fifth percentile for either of these measurements are potentially helpful in the diagnosis of severe malnutrition [37].

Bioelectric impedance analysis (BIA) is a safe procedure using electrodes attached to the patient or a special scale to measure body electrical conductivity and resistance as an estimate of body fat percentage and fat-free tissues. Studies evaluating the accuracy of BIA provide mixed results as it can be altered by physical activity, dehydration, diuretic use, and fluid retention. BIA is therefore controversial and currently not used in clinical practice [38, 39].
Dual energy X-ray absorptiometry (DEXA) can be used to validate the results of body composition obtained from anthropometry and BIA. It measures body composition utilizing a model that divides the body into distinct elements (bone, fat, lean, and bone-free lean mass) according to energy photons passing through the body [40]. Current guidelines suggest DEXA as a method for the diagnosis of malnutrition in liver disease [5]; in addition to its use in diagnosing osteoporosis and osteomalacia. DEXA is highly reproducible and is an accurate measurement of fat mass with fat variations of less than 1% [38]. It is less accurate in measuring lean mass, as fluid imbalances can alter X-ray passage [41]. Deuterium oxide dilution and in vivo neutron activation analysis (IVNAA) are two ancillary tests that are labor-intensive and not routinely available but are encouraged for use along with DEXA by the European Society for Clinical Nutrition and Metabolism for nutritional assessment in liver disease [5].

Handgrip strength is another potential assessment tool that is a sensitive predictor of malnutrition and the only method to predict major complications for cirrhosis at 1 year [42]. Measurement of strength is simple but requires a handgrip dynamometer. Furthermore, according to the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) Consensus, skeletal muscle is only well-associated in men and would not be a reliable tool in cirrhotic women as the degree of muscle loss from cirrhosis is gender-specific [31]. Use of handgrip strength as a measure of malnutrition in patients with liver disease therefore currently has limited clinical application.

Energy Expenditure

Resting energy expenditure (REE) should be considered for inclusion in the routine nutritional assessment of cirrhotic patients. The gold standard for measurement is indirect calorimetry (IC), but calculated estimations of an individual’s basic metabolic rate and daily kilocalorie requirements derived from tools such as Harris-Benedict’s equation can be used when IC is not available [5]. However, such equations have limitations as they are heavily influenced by variables such as weight, height, age, and gender. Using ideal body weight can underestimate energy requirements and actual weight may provide overestimation.
Current guidelines recommend using dry weight to account for fluid and volume shifts in cirrhotic patients as REE cannot be used in the presence of ascites as a contributor to body weight.

Establishing metrics for nutritional status in patients with ALD is important given the hypermetabolic state that leads to malnourishment and muscle wasting. In patients with alcoholic hepatitis, the measured energy expenditure per gram of creatinine is significantly increased, providing evidence of ALD as a hypermetabolic state [43] (Table 3).

Table 3
Guidelines for nutrition therapy in chronic liver disease

<table>
<thead>
<tr>
<th>Chronic liver disease</th>
<th>Protein (g/kg/day)</th>
<th>Energy (kcal/kg/day)</th>
<th>% Carbohydrates</th>
<th>% Lipids</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatohepatitis alcoholic</td>
<td>1.2–1.5</td>
<td>25–30</td>
<td>50–65</td>
<td>25–30a</td>
<td>Malignant or o ascenic Prognose</td>
</tr>
<tr>
<td>Alcoholic liver disease (ALD)</td>
<td>1.2–1.5b</td>
<td>35–40b</td>
<td>55–65</td>
<td>30–35a</td>
<td>Malignant Prognose</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>1.2–1.5</td>
<td>35–40</td>
<td>55–70</td>
<td>25–30a</td>
<td>Malignant Prognose</td>
</tr>
<tr>
<td>Compensated cirrhosis by:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein energy malnutrition (PEM)</td>
<td>1.5–1.8</td>
<td>35–50</td>
<td>72</td>
<td>28</td>
<td>Treated Malignant</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>1.0–1.5</td>
<td>30–40</td>
<td>73–80</td>
<td>20–27</td>
<td>Treated Malignant</td>
</tr>
<tr>
<td>Hepatic encephalopathy (HE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mecal Malignant</td>
</tr>
<tr>
<td>From [44, 45]</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*aPreference for polyunsaturated fatty acids

*bRecommendations from *American Association for the Study of Liver Diseases*
<table>
<thead>
<tr>
<th>Chronic liver disease</th>
<th>Protein (g/kg/day)</th>
<th>Energy (kcal/kg/day)</th>
<th>Total energy intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2–1.6 80% of</td>
<td>25–40</td>
<td>60–75</td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>Vegetable protein + dairy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>0.6 + 0.25 BCAA</td>
<td>25–40</td>
<td>60–75</td>
</tr>
</tbody>
</table>

Specific conditions Clinics:
Liver transplantation

Pre-transplant 1.2–1.75 35–40 70–80 20–30 Residual nutrient status
Post-transplant 1.2–1.5 30–35 >70 ≤30

From [44, 45]

*aPreference for polyunsaturated fatty acids

*bRecommendations from *American Association for the Study of Liver Diseases*

### Nutritional Deficiencies in Alcoholic Liver Disease

Patients with chronic liver disease are at risk for depletion of various fat-soluble and water-soluble vitamins with resultant symptoms, signs, and complications [46, 47]. The most well-recognized micronutrient deficiencies related to alcohol overuse are vitamin B12 (cyanocobalamin), folate, and zinc deficiencies.

### Vitamin B Deficiencies

Vitamin B1 (thiamine), B2, B6, B9, and B12 deficiency has been recognized in ALD as there is known hepatic activation and transport of these water-soluble vitamins [1, 47, 48, 49, 50, 51]. Increased serum concentrations of total plasma homocysteine (tHcy) and methylmalonic acid (MMA) are the most sensitive markers for vitamin B12 deficiency. It is important to recognize that in states of chronic alcohol use, serum
Hcy levels are routinely elevated [52]. Interestingly, while vitamin B12 deficiency should always be considered, patients with ALD have been reported to have falsely elevated B12 levels due to the inclusion of endogenous metabolically inactive forms of cobalamin [53]. In these cases, it may be less helpful to measure serum B12 levels. Holotranscobalamin, which is the active form of cobalamin, has been reported to be more reliable as an early marker of vitamin B12 deficiency in alcoholics [51].

Folate Deficiency

ALD is widely known to be associated with folate deficiency. This is due to reduced dietary intake, intestinal malabsorption, reduced liver uptake and storage, and increased urinary excretion [53]. Folate deficiency may be present in 80% of patients with ALD but is not directly tied to the stage of liver disease [54]. With folate fortification of foods in the USA, the prevalence of folate deficiency may be as low as 19% in patients with all stages of ALD [55].

Not only do patients with ALD have reduced dietary intake of folate related to their risk for malnutrition, but they also have impaired ability to metabolize available folate. Folate is fundamental for hepatic methionine metabolism, regulating homocysteine levels, antioxidant defense, DNA assembly, and methylation reactions contributing to gene regulation [53]. The final metabolite of folate is S-adenosylmethionine (SAM), which is processed in the liver. In patients with advanced liver disease, there is a reduced ability to utilize available folate for production of SAM, which leads to reduced methylation of DNA, histones, and proteins. This effect on methylation has detrimental impacts on cell signaling and growth, possibly increasing the risk for liver injury and hepatocellular carcinoma [56].

Finally, patients who consume large quantities of alcohol have impaired intestinal folate transport. Animals given large quantities of alcohol had reduced folic acid transport at the level of the jejunal brush border [57, 58]. Humans fed folate-depleted diets with regular alcohol consumption had significantly reduced hepatic metabolism and storage of folate compared to patients fed the same diet without the addition of alcohol [59].
Zinc Deficiency

Dietary zinc deficiency can exacerbate ethanol-induced liver injury and steatosis due to impaired ability to mitigate oxidative stress. Supplementation of zinc may improve alcoholic endotoxemia and induce the activity of alcohol dehydrogenase while decreasing ethanol-induced oxidative stress, via reduced Cyp2e1 activity [60].

The impact of zinc deficiency in patients with cirrhosis awaiting liver transplantation was assessed in 368 subjects separated into two groups with either low or normal zinc serum levels. Low-serum zinc levels were found to be highly associated with decreased liver function and a high Model for End-Stage Liver Disease (MELD) score. Furthermore, multivariate analysis demonstrated that low-serum zinc levels are an independent predictor for hepatic decompensation, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Patients with normal zinc levels had higher transplant-free survival compared to patients with low zinc levels. Reduced zinc levels in patients awaiting liver transplantation resulted in a 28.3-fold increased risk of death after transplantation [61].

There is evidence supporting the safety and efficacy of zinc supplementation for the improvement of endotoxemia, inflammatory biomarkers, and clinical status in patients with ALD. A randomized controlled clinical trial was performed to evaluate if 3 months of supplementation with 220 mg/day zinc sulfate would improve serologic biomarkers of liver injury, inflammation, and clinical status in patients with alcoholic cirrhosis. A total of 22 patients with mild to moderate alcoholic cirrhosis were randomized to receive zinc supplementation or placebo with 10 volunteers without a history of alcohol serving as controls. At baseline, patients with alcoholic cirrhosis had increased mean serum lipopolysaccharide (LPS), TNF-α, IL-6, IL-8, and decreased zinc than the placebo or control group. In addition, the mean zinc, LPS, TGF-β, TNF-α, IL-18, and Child-Pugh was significantly improved in the zinc group after at 3 months with no adverse effects reported [62, ••, 63].
Dietary Interventions

Patients hospitalized due to ALD often have interrupted oral feeding due to altered mental status and fasting for medical procedures or diagnostic tests. Fasting periods should remain as brief as possible to minimize the compounded effects of poor nutritional intake and catabolism that can lead to loss of muscle and decreased functional status [64•]. Small frequent meals and oral liquid supplements may help patients with ALD who have early satiety or abdominal distention due to ascites.

For inpatients consuming about 50% of hospital meals, dietary restrictions are often harmful and may contribute to malnutrition [9, 46]. Oral intake should be appropriate for each patient’s dentition [9]. Complications typical of liver disease such as upper gastrointestinal bleeding, hepatic encephalopathy, and sepsis can also lead to insufficient oral intake. Unfortunately, dietary management of encephalopathy with protein restriction is still recommended by some providers. Protein restriction along with fluid and sodium restriction for ascites can worsen nutritional status [46, 65]. Adjustment of medication administration such as shifted timing can help increase oral intake, especially if patients are fearful of eating due to frequent bowel movements related to lactulose administration for encephalopathy.

For patients with alcoholic cirrhosis, supplemental nutritional therapy may be needed to achieve the recommended 1.2–1.5 g/protein/kg/day and 35–40 kcal/kg/day [4, 66 6••, ]. Nutritional support is strongly advised if patients present with significant weight loss due to anorexia, malabsorption, and/or are expected to have a period of inadequate oral intake greater than 10 days.

Oral supplements can be useful adjuncts to increase calorie, protein, and vitamin-mineral intake and can improve hepatic encephalopathy as well as decrease occurrence of ascites and infection [7]. Patients with ALD often require supplementation with multivitamins containing folic acid and thiamine [67]. Therefore, vitamins and minerals such as vitamin A, vitamin D, vitamin E, selenium, magnesium, and zinc should be monitored and supplemented [44].
As zinc deficiency is the most common micronutrient deficiency in ALD, zinc supplementation can enhance the activity of alcohol dehydrogenase and suppress the isoform cytochrome P450 CYP2E, thereby potentially attenuating oxidative stress [66]. Administration of B-complex vitamins such as thiamine, folate, and pyridoxine is needed to prevent Wernicke encephalopathy [4, 44, 66, 68].

Nighttime nutritional supplementation with 700 kcal per day can improve lean muscle mass in patients with cirrhosis or alcoholic hepatitis [67]. In a randomized controlled trial, consumption of a nighttime snack by patients with cirrhosis resulted in an increase of 2 kg of lean tissue over 12 months. Before and after the intervention, patients had measurement of total body protein (TBP) by neutron activation analysis at baseline and at 3, 6, and 12 months. This change in lean muscle mass was not observed when the same enteral formula was provided during the day. Therefore, a late evening or bedtime snack is recommended to reverse anabolic resistance and sarcopenia in ALD with improvement in quality of life [9, 46]. However, the long-term effects of late evening nutritional supplementation on survival have not been established and require further investigation [9, 69].

Increased oxidative stress and oxidation of ingested lipids may also play a role in the pathogenesis of ALD. Dietary intake of saturated fat has been associated with decreased mortality, whereas intake of unsaturated fat has been associated with increased mortality [70]. In addition, animal and human studies also suggest that probiotic supplementation may reduce alcohol-induced hepatic inflammation by attenuating pro-inflammatory cytokines mediated by endotoxins derived from gram-negative intestinal bacteria in patients with ALD [71].

**Enteral and Parenteral Nutrition**

Nutritional support is important for both inpatients and outpatients with ALD [44, 46].

The goal of nutrition therapy is to provide substrates for liver regeneration and prevent, correct, and treat nutritional deficiencies and complications of liver disease. Nutritional interventions may also improve clinical outcomes after liver transplantation [64].
Enteral Nutrition

A retrospective cohort study demonstrated that 57% of 231 cirrhotic inpatients had malnutrition during their admission. However, only 16% received enteral nutrition during hospitalization. Moreover, only 8% received ongoing dietetic review and assessment following discharge, highlighting the need for adequate nutrition evaluation and follow-up for patients with ALD [72].

Decisions to initiate enteral nutrition therapy (EN) or total parenteral nutrition (TPN) after oral supplementation are not possible or sufficient and must consider the overall clinical condition of the patient and the relative risks and benefits of each modality of nutritional support. EN is preferred if there is adequate gastrointestinal motility and function as it is less invasive, more secure, and more efficient than parenteral means of nutrition [1, 45, 65].

In severe malnutrition, EN alone or in combination with PN should be started with consideration for early nasojejunal feeding to improve nutritional status, support liver function, reduce complications, and prolong survival. Benefits of EN in comparison to PN include preservation of intestinal barrier function with reduction of intestinal permeability, beneficial immunomodulation, and decreased risk of complications such as infections. Furthermore, EN has been shown to preserve muscle mass, prevent worsening sarcopenia, promote anabolism, and replace glutathione stores often depleted in those with ALD leading to decreased morbidity and mortality [65]. EN is indicated in patients hospitalized with acute alcoholic hepatitis [16]. All patients enrolled in both arms of the “Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH)” trial were provided nutritional support, underscoring the value of aggressive nutritional feeding in severe alcoholic hepatitis [73].

Implementing appropriate nutritional support for patients with ALD undergoing hepatobiliary surgery is crucial [19]. The recommended route of administration for perioperative patients is EN due to complications including infection associated with perioperative PN [4, 66 66, ].
In patients with alcoholic cirrhosis admitted with upper gastrointestinal bleeding, fasting should be minimized with resumption of nutrition following endoscopic hemostasis as soon as tolerated. In patients with bleeding from gastroesophageal varices, oral or enteral feeding can be safely initiated immediately following endoscopic therapy. The presence of nonbleeding esophageal varices which did not receive endoscopic intervention is not a contraindication for nasogastric tube placement [74].

In patients with ascites or coagulopathy, ostomy and percutaneous endoscopic gastrostomy (PEG) placement are contraindicated due to risk of bacterial peritonitis, hemorrhage, and leakage of ascitic fluid. The use of infusion pumps to administer tube feedings can improve tolerance to enteral supplementation and reduce abdominal discomfort, especially in patients with refractory ascites [1, 9].

EN formulas containing hydrolyzed soy-based protein or casein may be tolerated better than formulas containing other sources of protein. If tolerated and in the absence of intestinal malabsorption, polymeric or oligomeric formulas may be preferred [1, 9]. Formulations with high energy concentration and low sodium (40 mEq/day or less) are preferred for patients with ascites, to prevent or control fluid imbalance [1, 45]. Formulas with higher energy density (1.2 to 1.5 cal/ml) that contain all essential amino acids and micronutrients are recommended to promote weight gain and normalization of plasma levels of vitamins and trace elements [1, 45].

The effect of EN on mortality in ALD was evaluated in a multicenter study by Cabré E and colleagues (2000). Seventy-one patients with severe alcoholic hepatitis were randomized to receive either enteral tube feedings or daily administration of prednisone for 28 days and were followed up for 1 year or until death. Overall mortality was similar in both groups during follow-up, but early mortality was significantly higher in steroid-treated patients, primarily due to infection [6, ••, 67, 68, 75 •]. EN may also be beneficial with potential positive synergistic effects when combined with steroid therapy [5, 67, 76 6 ••].
A multicenter randomized controlled clinical trial was performed on 136 patients with biopsy-proven severe alcoholic hepatitis and receiving methylprednisolone to evaluate if enteral nutritional supplementation could improve mortality compared to a conventional hospital diet. EN (1500 kcal, 75 g protein, 170 g carbohydrates, and 58 g fat per 1000 mL of formula) was administered via feeding tube for 14 days. The catheter for enteral feeding was prematurely removed in 48.5% of patients, and among those, the median duration of tube feeding was only 5 days. Serious adverse events related to EN only occurred in 8% of patients, and the total number of infections did not differ significantly between the two groups. The cumulative mortality rate at 6 months did not differ between the groups and was 44% in the intensive EN group and 52.1% in the control group. However, regardless of the group assessed, patients receiving lower caloric intake (less than 21.5 kcal/kg/day) had a 65.8% mortality versus 33.1% mortality in patients with higher caloric intake. In addition, an improved 6-month survival was associated with intake of ≥65 g/day of lipids and ≥77.6 g/day of protein [77].

In most cases, patients with ALD who have mild or moderate hepatic encephalopathy can continue oral nutrition. EN via feeding tubes is indicated for those patients who develop advanced hepatic encephalopathy (grade 3 or grade 4) or for those who have limitations in maintaining oral intake [78].

Nutritional supplementation for 3–4 weeks has been associated with the resolution or improvement of hepatic encephalopathy. This underscores the safety and importance of adequate nutrition, including diets with adequate protein intake for patients with ALD and hepatic encephalopathy despite the continued practice by many providers of protein restriction in these patients [67].

Randomized controlled trials or systematic reviews have suggested that oral branched-chain amino acid (BCAA) supplementation can help achieve or maintain positive nitrogen balance in patients who are intolerant to dietary protein [6, ●●, 65, 79]. BCAA supplements have been associated with decreased frequency and severity of hepatic encephalopathy when prescribed as maintenance therapy [65, 79]. A
Cochrane systematic review evaluated 16 randomized clinical trials which included 827 participants with overt or minimal hepatic encephalopathy. Supplementation with BCAA was associated with improvement in hepatic encephalopathy, while there were no effects on mortality, quality of life, or measured nutritional parameters [80].

In contrast to supplementation with BCAA, glutamine supplementation should not be offered to patients with cirrhosis as it is metabolized to glutamate and ammonia [9]. A prospective study including 54 cirrhotic patients (63 % with alcoholic cirrhosis) was performed to evaluate the potential effect of glutamine on hepatic encephalopathy. The presence of hepatic encephalopathy was assessed by psychometric hepatic encephalopathy score 60 min before and after a 20-g oral glutamine load. After administration of glutamine, there was a significant increase in blood ammonia levels in cirrhotic patients, while there was no change observed in a group of healthy controls [81, 82].

Finally, compared to oral feeding, treatment of severe alcoholic hepatitis by EN via tube feeding has been associated with improvement of hepatic encephalopathy, plasma bilirubin, and markers of liver function [67].

In summary, nutritional therapy consisting of 30–35 kcal/kg daily and 1.2–1.3 g of protein/kg per day, as well supplementation with high dose of branched chain amino acids (0.25 g/kg/day), can reduce the frequency and severity of hepatic encephalopathy in patients with ALD [45].

Parenteral Nutrition

PN is indicated when nutritional needs cannot be met by an oral or enteral route. This is often the case in patients with small bowel or colonic obstruction [9].

It is important to monitor patients’ tolerance of glucose loads and lipid emulsion content to optimize tolerance of PN and the infusion of nonprotein calories. Periodic blood glucose levels and lipid profiles should also be evaluated. There is no need to modify the amino acid
content of formulations even in the presence encephalopathy provided that total protein load and patient mention are monitored [45, 65].

Patients with liver disease often have reduced synthesis of essential fatty acids which must be supplemented [81, 82]. Fat is fundamental in order to reach daily caloric recommendations but should not be more than 30–35% of total caloric intake. Stable patients with compensated cirrhosis generally tolerate a supply of lipids containing about 25–30% of nonprotein calories by means of conventional lipid emulsions with long-chain triglycerides (LCT) [65]. Furthermore, lipid emulsions or dietetic fat should not be restricted, unless delayed gastric emptying or true fat malabsorption has been diagnosed on fecal fat testing [65, 83].

If a patient with ALD develops cholestasis or steatorrhea, modification of TPN to lipid emulsions containing medium-chain triglycerides (MCT) that do not require bile salts for absorption may be considered. In patients with hypertriglyceridemia, lipid infusions can be restricted to once a week, but further study is needed [65]. Supplementation of ω3 fatty acids using fish oil lipid emulsion in combination with PN has also been suggested as a strategy to potentially delay graft injury, progression of recurrent liver cirrhosis, and infectious complications in post-transplant patients [84].

Increased risks of infection and infection-related mortality are associated with PN in patients with ALD. In addition, administering PN containing lipids carries a risk of steatohepatitis that can precipitate further hepatic decompensation [85].

A meta-analysis of 13 randomized controlled trials on nutritional therapy was performed with inclusion of 663 patients with alcoholic hepatitis and/or cirrhosis that were allocated to receive either EN or PN. Three hundred twenty-nine patients received EN or PN and were compared to 334 control patients who did not receive any nutritional intervention. Fixed-effect meta-analyses was performed and demonstrated that nutrition therapy may decrease the risk of hepatic encephalopathy and infection. Nutritional therapy may also reduce mortality in patients with alcoholic hepatitis or cirrhosis. However, subgroup analysis showed no significant differences in clinical
outcomes when comparing EN vs PN. Additional trials are still needed to determine the optimal dose and duration of nutrition therapy [6••].

In patients with ALD who develop hepatocellular carcinoma (HCC), factors such as chronic nausea, constipation, early satiety, and depression can impair adequate nutrition. Individualized nutritional counseling in these patients can promote the improvement of dietary intake, nutritional status, and quality of life. In HCC patients with poor appetite and early satiety, the prescription of megestrol acetate at doses between 160 and 1600 mg/day has been shown in randomized controlled trials to be associated with significant improvement in appetite, compared to placebo. However, nutritional support such as TPN has not been correlated with increased lean body mass in this population, and therapeutic decisions in this population must be considered in the context of their goals of care [86].

Conclusion

Malnutrition is associated with ALD and complications such as hepatic encephalopathy and infections. Adequate intake of calories, protein, and micronutrients with frequent meals and evening supplements and/or EN and PN when indicated has been associated with reduced mortality and morbidity. Finally, modification of protein/fat sources and composition in addition to probiotic supplementation are promising potential interventions for decreased progression of ALD and related complications.

Compliance with Ethical Standards

Conflict of Interest Drs. Chao, Waitzberg, Passos de Jesus, Bueno, Kha, Allen, Kappus, and Medici declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References
Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance


6. •• Fiorita AD, Israelensen M, Hamborg O, Krag A, Gluud LL. Nutritional therapy in cirrhosis or alcoholic hepatitis: a systematic review and meta-analysis. Liver Int. 2015;35(9):2072–8. This systematic review and meta-analysis included 13 randomized controlled trials evaluating the effects of enteral and intravenous nutrition therapy vs. no intervention in patients with cirrhosis or alcoholic hepatitis and suggests that nutrition therapy can lead to reduced mortality, overt encephalopathy and infection.


52. de Carvalho SC et al. Plasmatic higher levels of homocysteine in non-alcoholic fatty liver disease (NAFLD). Nutr J. 2013;12:37.


62. Mohammad MK, Falkner K, Song M, Craig J, McClain CJ, Cave MC. Low dose zinc sulfate (220mg) supplementation for three months normalizes zinc levels, endotoxemia, pro-inflammatory/fibrotic biomarkers & improves clinical parameters in alcoholic cirrhosis- a double-blind placebo controlled - (ZAC) clinical trial. Hepatology. 2015;62:851A. This single center double blind placebo controlled trial is the first to provide evidence for the safety and efficacy of zinc supplementation for improvement of endotoxemia, inflammatory biomarkers and clinical status in patients with alcoholic cirrhosis.


64. Bémeur C, Butterworth RF. Nutrition in the management of cirrhosis and its neurological complications. J Clin Exp Hepatol. 2014;4(2):141–50. This review summarizes the nutritional deficiencies commonly encountered in chronic liver disease and the impact that malnutrition can have on disease outcome,

incidence and severity of complications such as hepatic and Wernicke’s encephalopathy and post-transplant mortality and morbidity.


75. • Cabré E, Rodríguez-Iglesias P, Caballería J, Quer JC, Sánchez-Lombraña JL, Parés A, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multi-center randomized trial. Hepatology. 2000;32:3–42. This multicenter randomized compared the short and long term effects of total enteral nutrition vs. steroid therapy for 28 days in severe alcoholic hepatitis. Mortality was similar for both those treated with nutritional therapy and those treated with steroids during therapy, but occurred earlier in those treated with nutritional therapy. However, overall mortality at 1 year was higher in the group treated with steroids largely due to infection.


